IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	)	MDL Docket No. 2738
This Document Relates To All Cases	)	

DEFENDANTS JOHNSON & JOHNSON AND JOHNSON & JOHNSON CONSUMER INC.'S REPLY IN SUPPORT OF MOTION TO EXCLUDE PLAINTIFFS' EXPERTS' GENERAL CAUSATION OPINIONS

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In attempting to cast the parties' general causation positions as a "battle of the experts" that should be resolved by a jury and not the Court, plaintiffs' opposition brief ("Pls.' Opp'n") misrepresents the relevant science, defendants' arguments, their own experts' opinions and the law.

First, there can be no expert battle before a jury when one side has "failed to put forth competent evidence with which to create a conflict." *In re Baycol Prods. Litig.*, 596 F.3d 884, 892 (8th Cir. 2010). That is the case here. Because plaintiffs' experts engaged in results-oriented, methodologically flawed analyses, their opinions do not satisfy *Daubert* and cannot advance to a jury. Although plaintiffs point to a few talc rulings that found their general causation theories to be admissible, each of those was a perfunctory holding that failed to meaningfully analyze the relevant expert opinions. By contrast, the two courts that held hearings and did carefully evaluate the science ultimately determined that plaintiffs' evidence of causation was invalid. *See Carl v. Johnson & Johnson*, Nos. ATL-L-6546-14, ATL-L-6540-14, 2016 WL 4580145, at *19 (N.J. Super. Ct. Law Div. Sept. 2, 2016), *appeal pending*; *In re Johnson & Johnson Talcum Powder Cases*, No. BC628228, 2017 WL 4780572, at *19, *25 (Cal. Super. Ct. Oct. 20, 2017), *appeal pending*.

Second, plaintiffs fail to show that their experts conducted reliable Bradford Hill analyses. With respect to most of the Bradford Hill criteria (including strength,

dose response and biological plausibility), plaintiffs vacillate between trying to rewrite their experts' opinions and trying to write the criteria out of the Bradford Hill framework. And plaintiffs' heavy emphasis on consistency of association – elevating it above all else, as though satisfaction of this one factor would suffice to establish causation – is contrary to law. Indeed, at least one court in this Circuit has excluded purported Bradford Hill-based opinions that were similarly premised on the alleged satisfaction of just one factor. *See Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 514 (W.D. Pa. 2003) (excluding plaintiffs' expert's opinion where, among other things, "only one of the nine [Bradford Hill] criteria is satisfied in this case"). In any event, it is futile for plaintiffs to suggest that consistency is the be all and end all because they do not satisfy that criterion either. As set forth in defendants' opening brief, study results vary by type of study and population surveyed, and plaintiffs' experts' response – simply disregarding cohort studies and/or rejecting established statistical principles – is unscientific and unreliable.

Third, Dr. Smith-Bindman's conclusion that "regular" talc use is associated with a 50% increase in the risk of high grade serous invasive ovarian cancer ("HGSOC") was the product of a subjective and error-ridden post-hoc analysis. Plaintiffs' arguments only confirm that Dr. Smith-Bindman unreliably developed her conclusion before choosing which data to include, excluded studies that would

have refuted that conclusion and defined "regular" talc use in a manner that nobody (not even she) can make sense of.

Fourth, the scientific consensus and some of plaintiffs' experts' pronouncements outside litigation undermine their experts' causation opinions. Indeed, a paper co-authored by Dr. Jack Siemiatycki ***just last month*** did ***not*** list talc even as a ***suspected*** ovarian cancer risk factor. Plaintiffs respond by mischaracterizing defendants' argument, essentially ignoring the prior published views of their experts, Dr. Siemiatycki and Dr. Patricia Moorman, and suggesting that the science has strengthened in their favor over the last several years. These efforts to obscure reality should all be rejected.

For all of these reasons, discussed further below, plaintiffs' opposition brief does not succeed in resuscitating their experts' general causation opinions.

ARGUMENT

Plaintiffs' opposition brief attempts to cast the fringe, made-for-litigation theory that talc use causes ovarian cancer as a "battle of the experts" by distorting both *Daubert* law and the arguments in defendants' opening brief. This effort should be rejected.

I. PLAINTIFFS FUNDAMENTALLY MISCONSTRUE THE APPLICABLE STANDARD UNDER *DAUBERT*.

As a threshold matter, plaintiffs' opposition brief includes numerous misstatements about the applicable *Daubert* standard. Specifically, plaintiffs argue

that: (1) complex scientific issues should be left to the jury in derogation of the Court's gatekeeping role; (2) disagreements between the parties' experts' causation opinions implicate the weight of the evidence rather than its admissibility; and (3) flaws in studies relied upon by experts are also issues related to weight, not admissibility.[1] As set forth below, plaintiffs' arguments are not faithful to the applicable *Daubert* standard in any federal circuit – much less that of the Third Circuit – and should therefore be rejected.

First, plaintiffs' argument that courts should "cede complex issues to the jury"[2] is precisely backwards. As Justice Breyer explained in the seminal *Joiner* ruling, *Daubert* may require "judges to make subtle and sophisticated determinations about scientific methodology and its relation to the conclusions an expert witness seeks to offer – ***particularly when a case arises in an area where the science itself is tentative or uncertain***." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 147-48 (1997) (Breyer, J., concurring) (emphasis added). In other words, a district court's gatekeeping role is especially critical where – as here – experts are advancing unaccepted scientific theories that could lead to "crippling verdicts on

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[1] (*See, e.g.*, Pls.' Steering Committee's Omnibus Mem. of Law in Resp. & Opp'n to Defs.' Mot. to Exclude Pls.' General Causation Ops. ("Pls.' Opp'n") at 65-70, 80, 117-19, 164, 169-70, May 31, 2019 (ECF No. 9914) (corrected version of ECF No. 9888).)

[2] (*Id.* at 69.)

the basis of slender scientific evidence." *Perry v. Novartis Pharm. Corp.*, 564 F. Supp. 2d 452, 468 (E.D. Pa. 2008); *see also Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 596-97 (1993) ("[T]here are important differences between the quest for truth in the courtroom and the quest for truth in the laboratory" because "[s]cientific conclusions are subject to perpetual revision" while "[l]aw, on the other hand, must resolve disputes finally and quickly."). The notion that *Daubert* is somehow meant for simple issues whereas juries should decide complex issues would turn the very principles underlying the Supreme Court's rulings on their head.

Second, plaintiffs relatedly argue that "differing and competing expert opinions . . . are traditionally left for the jury."[3] But deferring to the jury every time experts disagree would similarly eradicate the district court's gatekeeping function. Instead, "district courts must evaluate proffered expert evidence in the first instance rather than leaving the task for the jury to sort through" and ensure that expert testimony satisfies the "minimum requirements of reliability." *See Lithuanian Commerce Corp. v. Sara Lee Hosiery*, 179 F.R.D. 450, 458-60 (D.N.J. 1998). Put another way, although district courts "should not . . . usurp the role of the fact-finder," they must exclude such evidence when "the flaw is large enough

[3] (Pls.' Opp'n at 69.)

that the expert lacks . . . 'good grounds' for his or her conclusions." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 792-93 (3d Cir. 2017) ("*Zoloft III*") (citation omitted). As one court in this Circuit court put it, the common argument that methodological flaws go to weight fails when the "flaws go to the core body of the proffered evidence." *Bruno v. Bozzuto's, Inc.*, 311 F.R.D. 124, 140 (M.D. Pa. 2015); *see also Citizens Fin. Grp., Inc. v. Citizens Nat'l Bank of Evans City*, 383 F.3d 110, 121 (3d Cir. 2004) (rejecting weight argument where the underlying "methodology was fundamentally flawed").

That is precisely the situation here, because plaintiffs' experts' errors implicate the core of the methodologies through which they purport to find causation. This stands in stark contrast to plaintiffs' critiques of defendants' experts' opinions, which consist of superficial caricatures of those opinions.[4] Accordingly, although there are cases where both sides' experts' opinions "fall[] within 'the range where experts may reasonably differ,'"[5] this is not one of them. *See, e.g.*, *In re Baycol Prods. Litig.*, 596 F.3d at 892 ("Without competent evidence on both sides, there can be no 'battle of the experts' in which a fact-finder could weigh competing claims. Simply put, this case presents us with

[4] (*See generally, e.g.*, Defs. Mem. of Law in Opp'n to Pls.' Mot. to Exclude Defs.' Epidemiology Experts ("Defs.' Epi. Opp'n"), May 29, 2019 (ECF No. 9871).)

[5] (Pls.' Opp'n at 70 (citation omitted).)

an expert opinion based on conclusory statements, weak scientific evidence, and temporal proximity in the face of alternative explanations.").[6]

Third, plaintiffs likewise claim that "challenge[s]" to expert opinions "based on there being 'flaws' in a study" also implicate the weight of the opinions rather

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[6] Plaintiffs relatedly argue that defendants' opening brief improperly cited to defendants' experts' reports, suggesting that such citations demonstrate that these are merely competing expert opinions to be resolved by a jury. (*See* Pls.' Opp'n at 83-84; *see also id.* at 76 (criticizing defendants for "liberally cit[ing] to [their] own experts").) As an initial matter, this argument is highly disingenuous given that plaintiffs themselves cited extensively to their own experts' opinions in their motions to exclude. (*See, e.g.*, Pls.' Steering Committee's Mem. of Law in Supp. of Mot. to Exclude the Ops. of Defs.' Epidemiology Experts Karla Ballman, Ph.D., Christian Merlo, M.D., MPH, Gregory Diette, M.D., MHS, and Jonathan Borak, M.D., DABT ("Pls.' Epi. Mot.") at 11 n.21, May 7, 2019 (ECF No. 9737-1) (citing reports of Drs. Siemiatycki and Smith-Bindman for proposition that there are multiple meta-analyses of the observational studies); *id.* at 12 n.22 (citing Dr. Siemiatycki's report for claim that 25-35% increased risk is similar to other causal relationships); *id.* at 69-71 nn.150-54 (citing reports and testimony of Drs. Moorman and Siemiatycki for proposition that relative risks are not objectively characterized); *see also* Pls.' Steering Committee's Mem. of Law in Supp. of Mot. to Exclude the Expert Ops. of Defs.' Molecular Biologists ("Pls.' Molecular Biologists Mot.") at 5 n.9, May 7, 2019 (ECF No. 9743-1) (citing Dr. Crowley's report for argument that there are multiple carcinogens in talcum powder); Pls.' Molecular Biologists Mot. at 7 n.12 (citing report of Drs. Longo and Rigler in support of claim that carcinogens have been in the Products for decades).) But more importantly, defendants cited their experts' reports to explain scientific concepts and identify flaws in the methodologies employed by plaintiffs' experts. As courts have recognized, this is "entirely appropriate." *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1368 (N.D. Fla. 2018) (it is "entirely appropriate" for defendants' experts to offer what are, "essentially, critiques of [p]laintiffs' experts' evidence, methodologies, and conclusions").

than their admissibility.[7] But courts routinely consider expert testimony heavily reliant on scientifically flawed studies to be a telltale sign of an unreliable methodology. *See, e.g.*, *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 464-65 (E.D. Pa. 2014) ("*Zoloft I*") (excluding expert who "d[id] not address" "significant issues with regard to . . . confounding factors" raised by a study and "other issues mentioned repeatedly in the literature"); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 607-08 (D.N.J. 2002) ("This [c]ourt cannot admit Dr. Ozonoff's testimony as reliably based on a scientific method" where he "relied most heavily" on a study that "had a huge confidence interval, indicating that the results of the study [were] unstable and imprecise."), *aff'd*, 68 F. App'x 356 (3d Cir. 2003); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1179 (N.D. Cal. 2007) (criticizing an expert for "rel[ying] heavily" on a study that "fail[ed] to adjust for critical compounding factors"); *see also Roche Palo Alto LLC v. Ranbaxy Labs. Ltd.*, No. 06-2003, 2009 WL 3261252, at *39 (D.N.J. Sept. 30, 2009) (Wolfson, J.) (in bench ruling, identifying numerous flaws in a study and rejecting expert's opinion in part for relying on the flawed study).

[7] (Pls.' Opp'n at 70-71.)

In pressing these overlapping arguments, plaintiffs repeatedly rely on a recent district court ruling admitting what it called "shaky" causation opinions in *In re Roundup Products Liability Litigation*, No. 16-md-02741-VC, 2018 WL 3368534 (N.D. Cal. July 10, 2018). But the *Roundup* ruling all but states that the general causation testimony in that litigation would have been excluded under Third Circuit law. *Id.* at *5 (explaining that the Ninth Circuit's decisions have "resulted in slightly more room for deference to experts in close cases than might be appropriate in some other Circuits," specifically citing the Third Circuit's *Zoloft III* decision as an example of a more exacting standard).[8] Particularly in light of the *Roundup* court's recognition that the proffered opinions in that litigation would likely not pass muster in the Third Circuit, plaintiffs' reliance on that ruling is

[8] Plaintiffs also cite *In re Testosterone Replacement Therapy Products Liability Litigation Coordinated Pretrial Proceedings*, No. 14 C 1748, 2017 WL 1833173 (N.D. Ill. May 8, 2017); and *In re Fosamax (Alendronate Sodium) Products Liability Litigation*, No. 11-5304, 08-08, 2013 WL 1558690 (D.N.J. Apr. 10, 2013). *In re Testosterone* is inapposite because there was much stronger evidence supporting causation in that litigation, including placebo-controlled randomized trials, which demonstrated a statistically significant association between testosterone replacement therapy and cardiovascular events. *See* 2017 WL 1833173, at *3. And in *Fosamax*, the body of evidence supporting causation included randomized controlled trials (which do not exist for talc), and the defendants primarily criticized the plaintiffs' experts for not explaining how they weighed different studies and for applying the Bradford Hill criteria to non-epidemiological studies – arguments not pressed here. *See* 2013 WL 1558690, at *4, *6.

fundamentally misplaced and does ***not*** support their bid to admit their experts' opinions in this litigation.[9]

Finally, plaintiffs also tout a handful of rulings deeming expert causation evidence admissible in other talc cases.[10] However, those outlier rulings should not have any bearing on the question of admissibility in this litigation because they did not involve the federal *Daubert* standard, they considered different evidence and arguments, and/or they did not seriously delve into the fundamental question of general causation. For example, plaintiffs highlight "several" Missouri cases that they claim were decided pursuant to an expert admissibility statute that

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[9] Defendants respectfully submit that *Roundup* was wrongly decided even under the prevailing law in the Ninth Circuit because the plaintiffs' experts' causation opinions in *Roundup* did not constitute "good science" given the facially weak epidemiological association – which the experts failed to overcome with any other strong indicia of causation. *See Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1316 (9th Cir. 1995) ("Our responsibility, then, . . . is to resolve disputes among respected, well-credentialed scientists about matters squarely within their expertise . . . as to what is and what is not 'good science,' and occasionally to reject such expert testimony because it was not 'derived by the scientific method.'"); *see also* Wynder et al., *Weak Associations in Epidemiology and Their Interpretation*, 11 Preventive Med. 464, 465 (1982) ("Wynder 1982") (attached as Ex. A157 to Certification of Julie L. Tersigni ("Tersigni Cert"), May 7, 2019 (ECF No. 9723-2).) ("the need to seek supporting evidence is greater with weak than with strong associations"). And in any event, *Roundup* is not on point because, unlike here, IARC had classified the chemical there as "probably carcinogenic." *See* 2018 WL 3368534, at *1.

[10] (*See* Pls.' Opp'n at 65-68.)

"substantively mirrors Fed. R. Evid. 702."[11] While it is true that Missouri recently adopted *Daubert*, the state court judge presiding over talc cases did not attempt to seriously apply it, instead issuing a summary oral ruling that made no scientific findings whatsoever. And the same lax approach was true of *Berg v. Johnson & Johnson*, No. 09-04179-KES, 940 F. Supp. 2d 983 (D.S.D. 2013), and *Brower v. Johnson & Johnson, Inc.*, No. 16-EV-005534-E (Ga. Fulton Cty. Mar. 26, 2019),[12] in which the courts permitted the plaintiffs' experts to testify on general causation with little or no analysis of the science behind plaintiffs' theories or the methods employed by their experts.

By contrast, the courts that have actually addressed the evidence and the experts' reasoning in a serious and methodical fashion have deemed the science unsupportive of causation and opinions maintaining the contrary unreliable. *See Carl*, 2016 WL 4580145, at *18-19 (the talc studies showed a "uniformly weak . . . association" and plaintiffs' experts' "rigidly dismissive" approach to cohort studies was unreliable, especially in light of the accepted understanding that case-control studies are generally "less reliable than a prospective cohort study"); *In re Johnson*

[11] (*Id.* at 67.)

[12] (*See* Pls.' Opp'n at 66, 68 (citing Mem. Op. & Order, *Berg v. Johnson & Johnson*, CIV. 09-4179-KES (D.S.D. Apr. 12, 2013); Order on Defs.' Mot. to Exclude the Test. of Dr. James Barter, Dr. Laura Plunkett, and Dr. John Godleski, *Brower v. Johnson & Johnson, Inc.*, No. 16-EV-005534-E (Ga. Fulton Cnty. Mar. 26, 2019)).)

& Johnson Talcum Powder Cases, 2017 WL 4780572, at *19, *25 (verdict could not stand "given the lack of anything other than a hypothesis about causation and the nature of the epidemiological evidence presented"). The clear import of these carefully-reasoned opinions is that the theory that talc causes ovarian cancer is junk science. Accordingly, and in light of the robust *Daubert* standard that applies within the Third Circuit, the Court should follow the lead of these cases rather than the cursory, non-substantive rulings highlighted in plaintiffs' brief.

II. PLAINTIFFS' EXPERTS DISTORTED THE BRADFORD HILL FRAMEWORK, RENDERING THEIR OPINIONS UNRELIABLE AND METHODOLOGICALLY FLAWED.

Applying the proper standards, it cannot be denied that plaintiffs' experts' causation methodologies (while purportedly conducted pursuant to the Bradford Hill criteria) are unreliable and thus inadmissible under *Daubert* and *Zoloft* for numerous reasons set forth in defendants' opening brief and below. Plaintiffs' arguments to the contrary should be rejected.

A. Plaintiffs' Attempt To Downplay The Importance Of Strength Of Association Is A Tacit Admission That Their Experts Unreliably Evaluated It.

As set forth in defendants' opening brief, plaintiffs' experts' opinions that the strength consideration of the Bradford Hill framework is satisfied are unreliable because: (1) the association reported in the epidemiological literature is, at most, objectively low and weak; (2) this weak association may result entirely from non-

causal factors such as bias or confounding, which plaintiffs' experts brush aside unreliably; and (3) plaintiffs' experts improperly redefined strength by suggesting it is subject to public policy concerns and by invoking analogies to weak associations, such as secondhand smoke and lung cancer, that have been deemed causal.[13]

In replying to these arguments, plaintiffs demote the strength consideration behind consistency in their brief, failing to address it until page 131. This shuffling of factors is telling. Strength of association is traditionally the "first" factor analyzed in a Bradford Hill analysis,[14] in part because the magnitude of the association frames the remainder of the analysis: a weaker association should entail a more demanding showing on the other factors before a causal conclusion is reached.[15] As Hill succinctly put it, "First upon my list I would put the strength of

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[13] (Defs.' Mem. of Law in Supp. of Mot. to Exclude Pls.' Experts General Causation Ops. ("Defs.' Br.") at 31-46, May 7, 2019 (ECF No. 9736).)

[14] *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 255, 258 (S.D.N.Y. 2018) (describing strength as a "threshold factor"); *see also, e.g.*, *Zoloft III*, 858 F.3d at 795; *Magistrini*, 180 F. Supp. 2d at 592; *In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 187 (S.D.N.Y. 2009); *Jones v. Novartis Pharm. Corp.*, 235 F. Supp. 3d 1244, 1267 (N.D. Ala. 2017) (all addressing strength first).

[15] *See, e.g.*, Green et al., Fed. Judicial Ctr., *Reference Guide on Epidemiology*, in *Reference Manual on Scientific Evidence* 549, 602 (3d ed. 2011) ("Epidemiology Reference Manual") (attached as Ex. A51 to Tersigni Cert.) ("Although lower relative risks can reflect causality, the epidemiologist will ***scrutinize such associations more closely*** because there is a greater chance that

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association."[16] Plaintiffs' decision to put it lower on their list is a red flag that their experts did not reliably address it – as confirmed by plaintiffs' arguments, which in some parts contradict and in others fully abandon their own experts' reasoning.

1. Plaintiffs Cannot Refute That The Association In The Literature Is, At Best, Weak.

As explained in defendants' opening brief, the associations between 1.2 and 1.6 that are reported in the talc-ovarian cancer epidemiological literature are not supportive of causation because they are so close to 1.0 that the association could result entirely from non-causal factors such as bias or confounding.[17] As such, it is simply not reliable to opine – as plaintiffs' experts have done – that the association

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they are the result of uncontrolled confounding or biases.") (emphasis added). For this reason, plaintiffs' statement that "[a]s long as the risk is greater than 1.0, there is no minimal threshold for a causal relationship" (Pls.' Opp'n at 132) does not tell the whole story. While positive associations barely above 1.0 can be causative, that is only true when there are other very strong indicia of causation that ***overcome*** the weak association.

16 Hill, *The Environment and Disease: Association or Causation?*, 58(5) Proc. Royal Soc'y Med. 295, 295 (1965) ("Hill 1965") (attached as Ex. A63 to Tersigni Cert.).

17 (Defs.' Br. at 31-41.)

is "strong," or that "high weight" should be accorded this factor in the Bradford Hill analysis.[18] Plaintiffs' arguments in response lack merit.

First, plaintiffs begin their argument by eschewing the terms "strong and weak," but their own experts used these sorts of terms, and without these terms, there would be no way to conduct a Bradford Hill analysis. Indeed, plaintiffs' experts could not have been clearer that they considered the objectively weak association to be strong:

- Dr. Carson: "[T]hese epidemiological studies support a ***strong*** association between the perineal use of talcum powder and ovarian cancer."[19]
- Dr. Siemiatycki: "Thus, the 28% increase of ovarian cancer for women who used talcum powders is in line with many recognized risk factors. . . . Such a ***high and significant*** meta-RR could not have occurred by chance."[20]
- Dr. Singh: "I place significant weight on the fact that studies demonstrate a ***strong*** association between talcum powder use and ovarian cancer and show consistency of the data."[21]

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[18] (*See id.* at 32 & n.84 (citation omitted) (collecting plaintiffs' experts' descriptions of this factor, all indicating that they deem the factor strongly supportive of causation).)

[19] (Expert Report of Arch Carson, M.D., Ph.D. ("Carson Rep.") at 9, Nov. 16, 2018 (attached as Ex. C9 to Tersigni Cert.) (emphasis added).)

[20] (Expert Report of Jack Siemiatycki, M.Sc., Ph.D. ("Siemiatycki Rep.") at 62-63, Nov. 16, 2018 (attached as Ex. C21 to Tersigni Cert.) (emphasis added).)

[21] (Expert Report of Sonal Singh, M.D., M.P.H. ("Singh Rep.") at 63, Nov. 16, 2018 (attached as Ex. C40 to Tersigni Cert.) (emphasis added); *see also id.* at 17 (asserting that the "strength of association . . . is significant").)

- Dr. Moorman: "Taken as a whole, the ***overwhelming statistical strength*** of these studies, whose results are replicated over decades across a wide variety of populations and investigators, further supported by consistent meta-analysis, weighs very heavily in favor of a causal inference."[22]

- Dr. Smith-Bindman: "[A]ssessing *strength of association* when inferring causality requires examining underlying research and analytic methods, comparing the weight of evidence in the literature, and considering other contextual factors. The data supporting the causality of talcum powder products [sic] exposure for ovarian cancer is ***extremely strong***."[23]

While plaintiffs ***and several of their experts*** previously tried to justify these opinions on the ground that an association can be considered strong as a "public policy" matter even if it is quantitatively weak,[24] plaintiffs have abandoned that indefensible position. Instead, plaintiffs now accuse defendants of seeking to

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[22] (Expert Report of Patricia G. Moorman, M.S.P.H., Ph.D. ("Moorman Rep.") at 29, Nov. 16, 2018 (attached as Ex. C35 to Tersigni Cert.) (emphasis added).)

[23] (Expert Report of Rebecca Smith-Bindman, M.D. ("Smith-Bindman Rep.") at 37, Nov. 15, 2018 (attached as Ex. C36 to Tersigni Cert.) (emphases added).) It is even worse that a number of plaintiffs' experts find that the strength factor ***heavily*** supports causation. (*E.g.*, Carson Rep. at 9-10 (assigning strength the "most weight"); Expert Report of Anne McTiernan, M.D., Ph.D. ("McTiernan Rep.") at 63-64, Nov. 16, 2018 (attached as Ex. C7 to Tersigni Cert.) (increased risk of 22-31% "strongly supports a causal association" and given "high weight" in causation opinion); *see generally* Defs.' Br.; Siemiatycki Rep. at 63 ("This is a very important factor in how I view the evidence of causality, and it supports causality."); Expert Report of Ellen Blair Smith, M.D. ("Smith Rep.") at 21, Nov. 16, 2018 (attached as Ex. C16 to Tersigni Cert.) (strength of association among the "most important factors" for causation opinion).)

[24] (*See* Defs.' Br. at 42-43 & n.106 (noting that Drs. Smith-Bindman, McTiernan, Moorman, Smith and Clarke-Pearson each claim that a 1.2-1.6 relative risk should be deemed significant as a matter of policy).)

establish "arbitrary" thresholds of strong, moderate or weak associations when there is "no cut off value" at which an association cannot be indicative of a causal relationship.[25] In fact, there is nothing arbitrary about defendants' arguments. All defendants seek to highlight is that associations in the range of 1.2 to 1.6 are broadly recognized by the epidemiology community to be weak, and that it is well established that low associations often result from bias and confounding.[26] These are fundamental principles that cannot be refuted, and plaintiffs' experts' refusal to apply them properly reflects an unreliable methodology.

Second, plaintiffs take the position that the association between talc and ovarian cancer is not affected by recall bias and confounding, meaning that the strength of association is less of a concern. Not only is this speculative but the only available evidence is to the contrary. And while plaintiffs try to suggest this is a jury issue, not a *Daubert* issue,[27] that is simply not true because plaintiffs' experts' analyses of recall bias are one-sided and methodologically flawed.[28]

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25 (Pls.' Opp'n at 133-34 (citation omitted).)

26 (Defs.' Br. at 34-41.)

27 (Pls.' Opp'n at 78-79, 83-84.)

28 For example, Dr. McTiernan dismisses recall bias as "unlikely to be an issue" in a single paragraph and does not even mention it in her summary of case-control studies (McTiernan Rep. at 24, 41-42), yet extensively discusses "serious limitations to these cohort study analyses" when discussing cohort studies (*id.* at 46-47). (*See also, e.g.*, Smith-Bindman Rep. at 17, 20-21, 29-30 (similarly

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Recall bias. Plaintiffs' experts' opinions that any recall bias in the relevant studies would be "minimal" are highly unreliable ipse dixit, as set forth in defendants' opening brief.[29] And such ipse dixit, which is never admissible, is particularly unreliable in this circumstance because there is strong evidence that recall bias ***was*** at play in the talc case-control studies. As defendants explained in their opening brief, the Schildkraut 2016 case-control study (co-authored by Dr. Moorman) directly tested for recall bias and found that it was a significant concern. In particular, women interviewed after an increase in publicity regarding talc litigation reported a 15% higher rate of talc use, resulting in a ***2.5 times higher*** relative risk.[30]

Plaintiffs try to minimize Schildkraut by focusing on one phrase in that study, where the authors express skepticism that recall bias would "account for the

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providing muted recognition of recall bias in comparison to lengthy discussion of theorized weaknesses in cohort studies); Singh Rep. at 54-55 (similar); *see generally* Expert Report of Laura M. Plunkett, Ph.D., DABT. ("Plunkett Rep."), Nov. 16, 2018 (attached as Ex. C28 to Tersigni Cert.) (not mentioning recall bias).)

[29] (Defs.' Br. at 36; *see also*, *e.g.*, McTiernan Rep. at 24; Singh Rep. at 54; Siemiatycki Rep. at 54-55 (all discounting recall bias).)

[30] (Defs.' Br. at 36 (citing Schildkraut et al., *Association Between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study*, 25(10) Cancer Epidemiol Biomarkers & Prev. 1411, 1414 tbl. 2 (2016) ("Schildkraut 2016") (attached as Ex. A129 to Tersigni Cert.)).)

association" reported in talc studies before 2014.[31] But since their study did not find a statistically significant association between talc use and ovarian cancer before 2014, the Schildkraut authors were speculating when they put this statement in their paper. And both Drs. Moorman and Siemiatycki have previously stated in their publications that recall bias is a "concern" when it comes to talc case-control studies and "cannot be ruled out."[32]

Plaintiffs relatedly accuse defendants and their experts of "rank speculation" for suggesting that pre-2014 study participants could well have been exposed to reports about the talc controversy.[33] This argument fails for several reasons. For

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31 (Pls.' Opp'n at 145.)

32 Langseth et al., *Perineal Use of Talc and Risk of Ovarian Cancer*, 62 J. Epidemiology & Cmty. Health 358, 358 (2008) (attached as Ex. A88 to Tersigni Cert.) ("Langseth 2008") (meta-analysis co-authored by Dr. Siemiatycki); Peres et al., *Racial/ethnic differences in the epidemiology of ovarian cancer: a pooled analysis of 12 case-control studies*, Int'l J Epidemiol. 1, 10 (2017) (attached as Ex. A111 to Tersigni Cert.) (case-control study co-authored by Dr. Moorman stating that recall bias is a "concern" for variables such as "body powder exposure" that require study subjects to remember and report past events). Plaintiffs' reliance on Langseth 2008 and the IARC 2010 Monograph for the proposition that the risk of recall bias is "minimal" is misplaced. (Pls.' Opp'n at 142 n.388, 146 n.394.) Both sources recognized that recall bias "cannot be ruled out." *See* Langseth 2008; Int'l Agency for Research on Cancer, World Health Org., 93 Monographs on the Evaluation of Carcinogenic Risks to Humans: Carbon Black, Titanium Dioxide, and Talc 409 (2010) ("IARC 2010 Monograph") (attached as Ex. A72 to Tersigni Cert.) ("recall bias was a possibility inherent in the case-control studies and could not be ruled out").

33 (Pls.' Opp'n at 147-48 n.397.)

one thing, it is plaintiffs' burden to show that their experts' opinions have a reliable basis – not defendants' burden to "prove" recall bias.[34] In any event, defendants ***did*** show that extensive media coverage of the talc controversy preceded 2014. Plaintiffs discount this evidence, claiming that defendants' experts only produced a "handful" of articles before 2014.[35] But Dr. Diette made clear that he was only listing a "[s]ample" of articles, and in fact, he listed 38,[36] far more than the "handful" referenced by plaintiffs. In any event, these arguments also ignore that exposure to news reports is only part of the recall bias picture, as explained in defendants' opening brief.[37]

Plaintiffs (like their experts) also incorrectly argue that their experts' dismissal of recall bias is supported by the fact that "talcum use was differentially

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[34] Plaintiffs similarly argue that recall bias could not "have affected patients in other countries," but this too is wrong. (*Id.* (emphasis omitted).) News coverage of the talc controversy has spanned the globe for decades. *See, e.g.*, Doyle, *Talcum Powder May Cause Cancer*, The Scotsman (Edinburgh, Scotland), Oct. 22, 1997 (attached as Ex. A184 to 2d Suppl. Certification of Julie L. Tersigni ("2d Suppl. Tersigni Cert.")); McArthur, *Powder a Risk for Women*, Herald Sun (Australia), Feb. 20, 2009 (attached as Ex. A190 to 2d Suppl. Tersigni Cert.).

[35] (Pls.' Opp'n at 147 n.397.)

[36] (Sample of Pre-2014 News Articles Addressing Posited Link Between Talc Use and Ovarian Cancer (App. A to Expert Report of Gregory Diette, M.D., M.H.S. ("Diette Rep."), Feb. 25, 2019 (attached as Ex. C18 to Tersigni Cert.)).)

[37] (Defs.' Br. at 37.)

associated with some histological subtypes of ovarian cancer and not others."[38] But case-control studies have reported elevated risks for all or most ovarian cancer subtypes – not just HGSOC.[39] And plaintiffs do not have any support for the notion that recall bias would "[a]ffect[] all subtypes equally."[40] In fact, HGSOC – the subtype plaintiffs contend shows a higher elevated risk than all the others – is

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38 (Pls.' Opp'n at 147; *see also* Singh Rep. at 54 (same argument).)

39 *See, e.g.*, Schildkraut 2016 at 1414 tbl. 3 (respective ORs of 1.38 and 1.63 for serous and non-serous ovarian cancers); Merritt et al., *Talcum Powder, Chronic Pelvic Inflammation and NSAIDs in Relation to Risk of Epithelial Ovarian Cancer*, 122 Int'l J. Cancer 170, 172 tbl. II (2008) (attached as Ex. 43 to Pls.' Opp'n) (ORs ranging from 1.08 to 1.21 for the serous, mucinous endometrioid and clear cell subtypes); Chang & Risch, *Perineal Talc Exposure and Risk of Ovarian Carcinoma*, 79(12) Cancer 2396, 2399 tbl. 3 (1997) (attached as Ex. 34 to Pls.' Opp'n); Harlow et al., *Perineal Exposure to Talc and Ovarian Cancer*, 80(1) Obstet Gynecol. 19, 23 tbl. 5 (1992) (attached as Ex. A55 to Tersigni Cert.) (both similar); *see also, e.g.*, Cramer et al., *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*, 27 Epidemiol. 334, 342 tbl. 4 (2016) ("Cramer 2016") (attached as Ex. A25 to Tersigni Cert.); Mills et al., *Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California*, 112(3) Int'l J. Cancer 458, 461 tbl. III (2004) (attached as Ex. A94 to Tersigni Cert.); Cook et al., *Perineal Powder Exposure and the Risk of Ovarian Cancer*, 145(5) Am. J. Epidemiol. 459, 464 tbl. 5 (1997) (attached as Ex. A21 to Tersigni Cert.) (all reporting elevated RRs for most subtypes). As defendants have explained, the ovarian cancer subtypes are so different that they are considered different diseases altogether. Accordingly, these studies show the precise sort of "systematically . . . elevated RRs" that plaintiffs' experts argue ***would*** demonstrate recall bias. (*See* Siemiatycki Rep. at 54.)

40 (Pls.' Opp'n at 146 (emphasis omitted).)

also the most aggressive and lethal form of ovarian cancer.[41] Patients with a particularly deadly disease may be more likely than others to over-report past talc use, amplifying the effect of recall bias.[42]

Confounding. Plaintiffs' attempt to defend their experts' ostensible consideration of confounding likewise fails. Plaintiffs highlight their expert Dr. Moorman's statement that "'[t]o [her] knowledge, in the more than 30 years of research on talc and ovarian cancer no such confounder has been identified that could account for the increased risk with talc use.'"[43] But defendants and their experts did identify "such [a] confounder" – douching, which nearly doubled the risk of ovarian cancer according to one cohort study and was also shown to be correlated with talc use.[44]

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41 (*E.g.*, Expert Report of Benjamin Neel, M.D., Ph.D. ("Neel Rep.") at 10, Feb. 25, 2019 (attached as Ex. C10 to Tersigni Cert.) ("The most common EOC, high grade serous ovarian carcinoma (HGSOC), is, unfortunately, also the most lethal gynecologic malignancy and the 5th-most-common cause of cancer death in women in the United States.").)

42 (*See* Defs.' Br. at 37 (explaining that recall bias results in part from sick patients' propensity to search (consciously or subconsciously) for past events that could have caused their disease).)

43 (Pls.' Opp'n at 149 n.399, 150 (quoting Moorman Rep. at 28-29).)

44 Gonzalez et al., *Douching, Talc Use, and Risk of Ovarian Cancer*, 27(6) Epidemiol. 797, 800-01 (2016) ("Gonzalez 2016") (attached as Ex. A47 to Tersigni Cert.) (concluding that douching and talc use "are correlated" and that "[e]ver douching during 12 months prior to study entry was associated with" a statistically significant 1.8 hazard ratio for ovarian cancer); *see also* Rosenblatt et

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Given the evidence that at least one confounding variable correlated with talc use is associated with an increased risk of ovarian cancer, it was especially important for plaintiffs' experts to show that the reported talc association is not spurious. *See, e.g.*, *In re Mirena*, 341 F. Supp. 3d at 262.[45] But only Dr. Moorman addressed douching, and her explanations are not credible for the reasons explained in defendants opening brief. For example, Dr. Moorman points to a sensitivity analysis in Gonzalez 2016 that she contends showed that controlling for douching "had a negligible effect on the association" for talc.[46] But the Gonzalez authors disagreed, concluding that "behavioral correlation between talc use and

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al., *Characteristics of Women Who Use Perineal Powders*, 92(5) Obstetrics & Gynecology 753, 754 (1998) (attached as Ex. A124 to Tersigni Cert.) ("A relatively higher proportion of women who used [talcum] powder . . . also had douched . . ., consumed alcohol . . ., or smoked cigarettes. Women in the highest BMI were relatively more likely ever to have used powder in the perineal area"); Houghton et al., *Perineal Powder Use and Risk of Ovarian Cancer*, 106(9) J. Nat'l Cancer Inst. at 3 (2014) ("Houghton 2014") (attached as Ex. A65 to Tersigni Cert.) (similarly observing that talc users are more likely than nonusers to have a number of risk-increasing characteristics).

[45] Plaintiffs argue that "this case does not rest on the interpretation of a single study" because there "are literally dozens of ta[l]c studies spanning 40 years." (Pls.' Opp'n at 150.) But defendants showed that only a couple of case-control studies have accounted for douching. (Defs.' Br. at 38-39.) Plaintiffs ignore this point.

[46] (Pls.' Opp'n at 152 (discussing Moorman Rep. at 28).)

douching ***could produce confounding***."[47] Plaintiffs ignore this part of the study, even though it was addressed in defendants' opening brief.[48]

In any event, douching is only one potential confounder. As defense expert Dr. Christian Merlo explained, other known potential confounders include the number of pregnancies and a woman's age at each pregnancy, menopausal status and age at menopause, breastfeeding, whether the case-control study was hospital-based or community-based, exercise, hair dye use and use of other medications.[49] The consideration of these and other confounders "varied widely among the case-control studies from no adjustment for potential confounders to adjusting for varying degrees of confounding."[50] This, too, highlights why the weak association between talc use and ovarian cancer is suspect – and why it was irresponsible and unreliable for plaintiffs' experts to pretend that the association is actually strong.

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47 Gonzalez 2016 at 797 (background) (emphasis added).

48 (Defs.' Br. at 40 n.105.)

49 (Expert Report of Christian Merlo, M.D., M.P.H. ("Merlo Rep.") at 13, Feb. 25, 2019 (attached as Ex. C13 to Tersigni Cert.).)

50 (*Id.*)

2. The Fact That Some Causal Relationships Have Weak Associations Does Not Make The Association Here Strong.

As defendants explained in their opening brief, plaintiffs' experts' position that some causal relationships have been established despite low associations does not make the association here strong.[51]

In response, plaintiffs argue that their experts drew these analogies "for one purpose only—to demonstrate concretely that the strength of association aspect . . . need not exceed 2.0 before a causal association can be reached."[52] But defendants have never contended that 2.0 is a threshold for general causation or that weak associations can never be causal. There could be (and indeed, there are) some circumstances where the other Bradford Hill factors are so compelling that strength becomes less important. Here, however, plaintiffs' experts did not take the position that even though the association is weak, other factors are so strong that this factor is not dispositive. (Nor could they have, since the other factors were not satisfied either.) Instead, they took the demonstrably false position that the strength factor was satisfied and then justified that approach by noting that other

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51 (Defs.' Br. at 43-46 (addressing these arguments by Drs. Moorman, Siemiatycki and Singh).)

52 (*Id.* at 140.)

weak associations have been proven to be causal.[53] That is completely illogical and highlights the results-oriented nature of their opinions.

For all of these reasons, plaintiffs' defenses of their experts' unreliable assessment of strength of association are meritless.

B. The Epidemiology Is Inconsistent, And Plaintiffs' Experts' Efforts To Show Otherwise Should Be Rejected.

Plaintiffs spend a whopping 40 pages of their brief addressing "consistency," using this factor as a springboard to attack scientific norms concerning the hierarchy of evidence and statistical significance. But those 40 pages fail to rebut the simple truth: the studies are inconsistent.

As defendants have previously explained, the cohort studies do not show any association between external talc use and ovarian cancer, while the case-control studies varied both by study design and even within the category of population-based studies.[54] Hill could not have been clearer in defining consistency: studies should yield "similar results" that have been "reached in quite different ways, e.g.,

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[53] (*See id.* at 43 n.108 (identifying Drs. Moorman, Siemiatycki and Singh as pointing to other exposures that have been deemed to cause diseases despite low relative risks).)

[54] (Defs.' Br. at 47.)

prospectively and retrospectively."[55] That consideration is not satisfied by the study results here.

Plaintiffs' threshold response is to contend that the scientific community has concluded that these studies are nevertheless consistent.[56] Not so. Of the sources plaintiffs cite in support of this proposition, one (the FDA) directly contradicts it;[57] the second (the Institute of Medicine) does not address consistency at all;[58] and the third (Health Canada) refers to an underlying meta-analysis by Taher and others that expressly acknowledges that an association has been reported in "[c]ase-control studies but not in cohort studies."[59] It is thus plaintiffs, not defendants, whose position contravenes the scientific consensus.

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55 Hill 1965 at 297 (emphasis added); *id.* at 296 (further defining this criterion as whether an association "[h]as . . . been repeatedly observed by different persons, in different places, circumstances and times"); *see also* Epidemiology Reference Manual at 604 ("Different studies that examine the same exposure-disease relationship generally should yield similar results.").

56 (Pls.' Opp'n at 92-94.)

57 Letter from Steven M. Musser, Ph.D., Deputy Dir. for Sci. Operations, Ctr. for Food Safety & Applied Nutrition, to Samuel S. Epstein, M.D., Cancer Prev. Coalition, Univ. of Ill. – Chi. School of Pub. Health, at 4 (Apr. 1, 2014) ("FDA Denial Letter") (attached as Ex. A89 to Tersigni Cert.) ("Results of case-control studies do not demonstrate a consistent positive association across studies.").

58 The IOM report uses the words "talc" and "talcum" collectively three times in more than 300 pages and, unsurprisingly, does not address the issue of consistency in epidemiologic studies of external talc use.

59 Taher et al., *Systematic Review and Meta-Analysis of the Association Between Perineal Use of Talc and Risk of Ovarian Cancer*, at 25 tbl. 2

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Plaintiffs' other arguments, which essentially call on the scientific community to discard the concepts of statistical significance and the hierarchy of epidemiologic evidence, fail as well.

1. Plaintiffs Fail To Justify Their Experts' Rejection Of The Results Of The Cohort Studies.

As explained in defendants' opening brief, plaintiffs' experts' various efforts to nullify the findings of the cohort studies – by attacking their size, follow-up periods and ascertainment of exposure, and in the case of some experts, the Gates 2010 study in its entirety – all lack a reliable basis.[60] Plaintiffs remarkably do not respond to these arguments; instead they simply echo the conclusions that their experts purported to reach, without attempting to address the serious flaws in the reasoning their experts used to reach those conclusions.[61] Because plaintiffs' experts' reasoning was unreliable – and because their justification for ignoring the results of cohort studies rests entirely on this flawed reasoning – this is an issue that goes to admissibility, not weight, and the Court should accordingly exclude

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(unpublished, 2018) ("Taher 2018") (attached as Ex. A137 to Tersigni Cert.); *see also* Health Canada, Draft Screening Assessment: Talc ($Mg_3H_2(SiO_3)_4$) (Chem. Abstracts Serv. Registry No. 14807-96-6), at 19-20 (2018) ("Draft Screening Assessment") (attached as Ex. A58 to Tersigni Cert.).

[60] (Defs.' Br. at 50-61 (addressing opinions offered by Drs. McTiernan, Carson, Moorman, Siemiatycki, Singh, Wolf, Smith, Clarke-Pearson and Smith-Bindman).)

[61] (*See* Pls.' Opp'n at 119-24.)

plaintiffs' experts' opinions. *See, e.g.*, *Bruno*, 311 F.R.D. at 140; *Zoloft III*, 858 F.3d at 792-93 (exclusion appropriate where "the flaw is large enough that the expert lacks the 'good grounds' for his or her conclusions") (citation omitted).

The arguments plaintiffs do make in their brief with respect to the inconsistency between cohort and case-control studies all lack merit. ***First***, plaintiffs repeatedly contend that the cohort studies "showed a positive association," as if to suggest that they are not actually discordant with case-control studies.[62] Any such suggestion is baseless. It is undisputed that the cohort studies collectively reported a non-significant odds ratio of ***1.02***,[63] which is nowhere near the 25-45% "overall risk" that plaintiffs tout elsewhere in their brief.[64] And the four individual cohort studies reported odds ratios of 1.09,[65] 1.06,[66] 1.12[67] and

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[62] (*Id.* at 37, 76-66, 126; *see also id. at* 34, 91-92 ("The vast majority of these studies, regardless of study design, have shown a positive .").)

[63] Berge et al., *Genital Use of Talc and Risk of Ovarian Cancer: A Meta Analysis*, 27(3) Eur J Cancer Prev. 248, 251 (2018) ("Berge 2018") (attached as Ex. A11 to Tersigni Cert.).

[64] (*E.g.*, Pls.' Opp'n at 131.)

[65] Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*, 92 J. Nat. Cancer Inst. 249, 251 (2000) ("Gertig 2000") (attached as Ex. A45 to Tersigni Cert.).

[66] Gates et al., *Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype*, 171(1) Am. J. Epidemiol. 45, 45 (2010) ("Gates 2010") (attached as Ex. A42 to Tersigni Cert.).

[67] Houghton 2014 at 1.

0.73.[68] One of these is ***negative***, and although the other three are technically "positive," they are not statistically significant and so close to 1.0 that not even plaintiffs' experts consider them to be meaningful evidence of an association.[69] Indeed, plaintiffs' experts go to great lengths to highlight the alleged flaws of the cohort studies precisely because the results do not favor their litigation position.[70]

Second, plaintiffs also repeatedly assert that the cohort studies collectively reveal a statistically significant positive association for HGSOC – as if to argue that consistency is at least established as to that subtype of ovarian cancer, pointing to the "Penninkilampi (2018) meta-analysis of **cohort** studies," which they say "demonstrated a statistically significant increased risk of serous ovarian cancer."[71] But Penninkilampi did not include the Gates 2010 cohort study, which demonstrated that the increased risk of HGSOC initially reported in Gertig 2000

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68 Gonzalez 2016 at 800-02.

69 (*See, e.g.*, Moorman Rep. at 18 ("[T]he cohort studies do not show a statistically significant association for ever use of talc and ovarian cancer overall."); Smith Dep. 222:10-14 (Q. "None of the cohorts performed today have found an association, correct?" A. "That is true.").)

70 (*See, e.g.*, Moorman Rep. at 24-28 (pointing to various purported disadvantages of cohort studies); McTiernan Rep at 48 (devoting just 12 pages to a discussion of 27 case-control studies and almost six pages to a discussion of just four case-control studies).)

71 (Pls.' Opp'n at 101; *see also id.* at 126 ("Indeed, that reasonableness is strengthened because a meta-analysis of the cohort studies (Penninkilampi) has demonstrated a statistically significant increased risk of Serous Invasive Ovarian Cancer.").)

disappeared with ten additional years of study.[72] Defendants explained at length why Gates 2010 should not be excluded from an analysis of the cohort studies (and why it is thus unreliable to rely on Penninkilampi's analysis that omitted it) – but plaintiffs do not respond. *See Magistrini*, 180 F. Supp. 2d at 607 (criticizing an expert for relying heavily on a flawed study while failing to sufficiently address the study's flaws).[73] Notably, the Berge meta-analysis, which did consider Gates,

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[72] Penninkilampi & Eslick, *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*, 29 Epidemiol. 41, 46 (2018) ("Penninkilampi 2018") (attached as Ex. A109 to Tersigni Cert.). (*See* Defs.' Br. at 15-16.)

[73] Another misrepresentation plaintiffs repeatedly make is their contention that "the majority of studies show a stati[sti]cally significant increase[d] risk between the genital use of talcum powder and epithelial ovarian cancer." (Pls.' Opp'n at 99 (emphasis omitted); *see also id.* at 3, 34, 91, 93, 108.) In fact, a majority of studies ***did not*** produce statistically significant results, although this issue is not clear-cut because it depends on which studies are considered, and in particular how earlier studies that were subsumed by later ones are counted. (*See* Pls.' Opp'n at 32 n.116 (omitting Cramer, *Conditions Associated with Antibodies Against the Tumor Association Antigen MUC1 and Their Relationship to Risk for Ovarian Cancer*, 14(5) Cancer Epidemiol, Biomarker Prev. 1125 (2005) (not statistically significant, which was subsumed by Cramer et al., *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*, 27(3) Epidemiol. 334 (2016)) but counting both Pike et al., *Hormonal Factors and the Risk of Invasive Ovarian Cancer: A Population-Based Case-Control*, 82(1) Fertility & Sterility 186 (2004) and Wu et al., *Markers of Inflammation and Risk of Ovarian Cancer in Los Angeles County*, Int J Cancer 1409 (2009) (statistically significant but subsumed by Wu et al., *African Americans and Hispanic Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates*, 24(7) Cancer Epidemiol Biomarkers Prev. 1094 (2015))).) Regardless, whether technically a slight majority or minority of studies report statistically significant associations is beside

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concluded that there was no statistically significant association in the cohort studies.[74]

Third, plaintiffs attempt to brush aside defendants' entire argument on consistency by arguing (incorrectly) that defendants' position is based on the hierarchy of evidence, which generally views cohort studies as stronger than case-control studies. This argument fails first and foremost because the premise is mistaken – regardless of whether cohort studies are generally more reliable than case-control studies, the consistency criterion is not satisfied because, *inter alia*, the two different types of studies yielded inconsistent results.[75] For this reason, plaintiffs' discussion of publications (mostly by Dr. Rothman) that address the hierarchy of epidemiological evidence is irrelevant.[76]

In any event, as defendants have explained in their prior briefing, the hierarchy of epidemiological evidence ***is*** well established, and Dr. Rothman's various writings acknowledge that reality even as he seeks to challenge the status

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the point. Either way, this is another area of substantial conflict, which, although not dispositive, disfavors a finding of consistency.

74 (*See* Defs.' Br. at 20.)

75 (Pls.' Opp'n at 114.)

76 (*Id.* at 128-31.)

quo.[77] Although plaintiffs argue that "even the most basic epidemiology textbooks teach that there is not a rigid hierarchy,"[78] one of the textbooks they repeatedly cite explicitly places cohort studies above case-control studies in "rank[ing]" the different types of studies according to "the degree to which identical findings of a statistical association are likely to demonstrate a causal association" based on, *inter*

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77 (Defs.' Epi. Opp'n at 35-36.)

78 (Pls.' Opp'n at 114.)

alia, susceptibility to bias and confounding.[79] Courts[80] and numerous scientists[81] have recognized the same principle.[82] Plaintiffs also offer no response to this point.

2. Plaintiffs Distort Defendants' Arguments In Attempting To Defend Their Experts' Unreliable Treatment Of Statistical Significance.

As defendants explained in their opening brief, plaintiffs and their experts also disregard the inconsistency among studies by ignoring statistical

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[79] Oleckno, *Epidemiology: Concepts and Methods* 190 (2008) (attached as Ex. 143 to Pls.' Opp'n) (cited in Pls.' Opp'n at 113, 115, 167 and in Pls.' Epi. Mot. at 27, 49, 50, 58). In addition, the World Cancer Research Fund (with which Dr. McTiernan is affiliated) has published that "[t]he hierarchy of epidemiological evidence places *cohort studies* above *case-control studies*" and that "[c]ohort studies are likely to be the main source of evidence" due in part to their prospective design. World Cancer Res. Fund & Am. Inst. for Cancer Res., *Continuous Update Project Expert Report: Judging the Evidence* (2018) (attached as Ex. A153 to Tersigni Cert.).

[80] *See, e.g.*, *Carl*, 2016 WL 4580145, at *12, *19 (case-control studies "are considered less reliable than a prospective cohort study").

[81] *See, e.g.*, Langseth 2008 at 358 (study co-written by Dr. Siemiatycki explaining that a talc cohort study was "arguably the strongest study because of its partly prospective ascertainment of exposure"); Penninkilampi 2018 at 47 (case-control studies are "low-level evidence"); Narod, *Talc and Ovarian Cancer*, 141(3) Gynecol. Oncol. 410, at 2 (2016) (attached as Ex. A97 to Tersigni Cert.) (prospective studies such as cohort studies "are given greater weight" because they are "less prone to bias than case-control studies").

[82] (*See generally* Defs.' Br. at 9-11; Defs.' Epi. Opp'n at 32-36.) Contrary to plaintiffs' portrayal (Pls.' Opp'n at 127), defendants cited the Reference Manual only for the basic proposition that there is a general hierarchy of evidence (Defs.' Br. at 9) – which is an uncontroversial point that plaintiffs nevertheless contest (*see, e.g.*, Pls.' Opp'n at 37; Pls.' Epi. Mot. at 34-37).

significance.[83] This approach runs afoul of the Third Circuit's recent ruling in *Zoloft*, contravenes prevailing scientific practice and rests on assertions about the lack of statistical power in certain studies that lack a reliable basis.[84] Plaintiffs' arguments in response – which span almost 20 pages of their brief[85] – lack merit.

First, plaintiffs mischaracterize defendants' argument. Defendants did not argue, as plaintiffs contend, that statistical significance is a litmus test such that the lack of statistical significance in some studies ***alone*** means that there is no consistency.[86] Rather, as explained in defendants' opening brief and above, in undertaking the consistency analysis, an expert cannot simply ignore the statistically insignificant nature of purportedly positive results,[87] because doing so unscientifically "downplay[s] the possibility that [the insignificant positive results] support *no* association." *Zoloft III*, 858 F.3d at 799. Plaintiffs cannot deny that their experts committed this error in attempting (unsuccessfully) to reconcile the inconsistent results of the case-control and cohort studies; as they describe it, their

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83 (Defs.' Br. at 61& n.150 (identifying Drs. Siemiatycki, McTiernan, Singh and Plunkett as having disregarded statistical significance).)

84 (*Id.* at 61-66.)

85 (Pls.' Opp'n at 96-114.)

86 (*See id.* at 96, 102 (contending that defendants have argued that plaintiffs' experts "fail[ed] to perform a mechanical multiple-choice 'significance--yes' and 'significance--no' exercise").)

87 (Defs.' Br. at 63-64.)

experts rested on the supposed fact that the "non-significant risk ratios for the remaining studies, including the Cohort studies, ***were positive***."[88] But such an approach is highly unscientific because it effectively reads statistical significance out of those findings, committing precisely the kind of error that the Third Circuit made clear is emblematic of an unreliable methodology. Particularly given that some of those so-called "positive" results just barely crossed the neutral value of 1.0, plaintiffs' experts' disregard for the lack of statistical significance renders their opinions all the more unreliable.[89]

Second, plaintiffs alternatively contend that their experts ***did*** account for statistical significance by "assess[ing] [studies'] confidence intervals to see if they included the" roughly 1.25 aggregate point estimate.[90] But few, if any, of plaintiffs' experts actually considered the overlap of confidence intervals in their analysis of consistency;[91] rather, this is something plaintiffs' counsel came up with in deposing defendants' experts. Plaintiffs cite four of their experts' reports in

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88 (Pls.' Opp'n at 102-03 (emphases added); *see also* Siemiatycki Rep. at 64; McTiernan Rep. at 41-42, 44; Singh Rep. at 63; Plunkett Rep. at 49 (all purporting to find consistency based on generally positive results).)

89 (Defs.' Br. at 61; *see also* Merlo Dep. 313:18-24 (explaining that if he were to describe a 1.1 risk ratio as even "modest," he would "get laughed out of the room").)

90 (Pls.' Opp'n at 100-106; *see also id.* at 37.)

91 (Pls.' Opp'n at 102-06.)

claiming that their experts "noted that . . .[t]he confidence intervals reported for the remaining non-significant studies . . . overlapped 1.2-1.25," but none of the reports actually say that.[92] As previously explained, plaintiffs' counsel cannot defend their experts' opinions using logic the experts themselves did not employ. *E.g.*, *Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 672-73 (6th Cir. 2010) (rejecting counsel's effort to redefine the expert's opinion; the expert's "opinion cannot escape its own logic").

Moreover, focusing solely on whether confidence intervals overlap at 1.2 or 1.25 would not be a reliable method of evaluating consistency for a number of reasons. For one thing, confidence intervals can be exceedingly wide and varied (as is the case here), and accordingly may easily overlap each other or a given point estimate.[93] As a result, numerous statisticians have criticized the technique,

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[92] (*See id.* (citing McTiernan Rep. at 41-42; Siemiatycki Rep. at 64; Moorman Rep. at 29; Expert Report of Sarah E. Kane, M.D. ("Kane Rep.") at 23-25, Nov. 15, 2018 (attached as Ex. C38 to Tersigni Cert.)).) For example, in the excerpt plaintiffs quote, Dr. McTiernan found non-significant studies consistent with significant ones "because their relative risks" – not their confidence intervals – "were consistent with" the other studies. (McTiernan Rep. at 41-42.) If plaintiffs' experts believe that overlapping confidence intervals show consistency of association, they were under an obligation to disclose that view in their reports.

[93] Two talc studies from 2016 with barely overlapping confidence intervals illustrate this. *Compare* Gonzalez 2016 at 797 (cohort study reporting OR 0.73 (95% CI = 0.44-1.2)) *with* Cramer 2016 at 334 (case-control study reporting RR 1.33 (95% CI = 1.16-1.52)). Not even plaintiffs' experts seriously contend that these studies are consistent; rather, their approach is to unilaterally criticize the Gonzalez study.

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explaining, for example, that "it is erroneous to" assess studies' differences "based on overlapping confidence intervals" because confidence intervals can overlap even when their means are drastically different.[94] Nor does either the Federal

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(*See* Smith-Bindman Rep. at 21; Kane Rep. at 26; Smith Rep. at 15; Siemiatycki Rep. at 57; Singh Rep. at 51-53; Moorman Rep. at 29.)

[94] Knezevic, *StatNews* #73: *Overlapping Confidence Intervals and Statistical Significance*, Cornell Statistical Consulting Unit, Cornell University (Oct. 2008) (attached as Ex. A187 to 2d Suppl. Tersigni Cert.); Ryan & Leadbetter, *On The Misuse of Confidence Intervals For Two Means In Testing For the Significance Of the Difference Between the Means*, 1(2) J. Modern Applied Stat. Methods 473, 473 (2002) (attached as Ex. A194 to 2d Suppl. Tersigni Cert.) ("[c]omparing individual confidence intervals of two populations is an incorrect procedure for determining the statistical significance of the difference between two means," because confidence intervals overlap even when the means are significantly different); Knol et al., *The (mis)use of overlap of confidence intervals to assess effect modification*, 26(4) Eur J. Epidemiol. 253 (2001) (attached as Ex. A188 to 2d Suppl. Tersigni Cert.) (explaining that the difference in the risk ratios of 0.67 (95% CI: 0.59-0.75) and 0.83 (95% CI: 0.71-0.98) are significant at the 95% confidence interval level even though the 95% confidence intervals overlap); Schenker & Gentleman, *On Judging the Significance of Differences by Examining the Overlap Between Confidence Intervals*, 55(3) The Amer. Statistician 182, 182 (abstract) (2001) (attached as Ex. A195 to 2d Suppl. Tersigni Cert.) ("[E]xamining overlap . . . should not be used for formal significance testing unless the data analyst is aware of its deficiencies and unless the information needed to carry out a more appropriate procedure is unavailable."); Austin & Hux, *A Brief Note on Overlapping Confidence Intervals*, 36 J. Vasc Surg. 194, 194 (2002) (attached as Ex. A183 to 2d Suppl. Tersigni Cert.) (explaining that "95% confidence intervals can overlap . . . yet the two means can be significantly different from one another"); Payton et al., *Overlapping Confidence Intervals or Standard Error Intervals: What do they mean in terms of statistical significance?*, 3(34) J. Insect Science 1, 1 (2003) (attached as Ex. A192 to 2d Suppl. Tersigni Cert.) ("checking for overlap" is "extreme and creates extremely conservative comparisons, making it difficult to detect significant differences in means").

Reference Manual or Third Circuit decision plaintiffs cite endorse finding consistency simply because studies' confidence intervals include the aggregate point estimate. Indeed, this approach would be just as rigid as the "mechanical" "significance testing" plaintiffs exhaustively criticize because it would exclude other important considerations, including the variability in the range of confidence intervals and the number of them that include 1.0.[95] Thus, these sources generally point out that confidence intervals can provide useful information when viewed holistically.[96] And viewing the confidence intervals of the talc studies holistically only makes the studies' inconsistency more apparent, since the confidence interval ranges were extremely divergent.[97]

Third, plaintiffs' attacks on the concept of statistical significance are meritless. As an initial matter, only one of plaintiffs' experts (Siemiatycki)

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[95] (*See* Pls.' Opp'n at 102-03 (citing Kaye & Freedman, *Reference Guide on Statistics*, in *Reference Manual on Scientific Evidence* 211, 253 (3d ed. 2011); *DeLuca by DeLuca v. Merrell Dow Pharm., Inc.*, 911 F.2d 941, 948-49 (3d Cir. 1990)).)

[96] *See* Epidemiology Reference Manual at 576-81 (explaining that using confidence intervals and p-values are two different ways to measure statistical significance and pointing out that the former has the advantage of "display[ing] more information"); *DeLuca by DeLuca*, 911 F.2d at 948 (discussing a "less rigid approach in which researchers look at the confidence intervals produced by various studies" to assess "the range of possibilities consistent with the data").

[97] (*See* Merlo Rep. at 34-35 (chart showing that the talc studies' confidence intervals ranged from 0.04 on the low end to 6.58 on the high end).)

addressed these concepts in his report. Thus, plaintiffs cannot rely on this argument to defend the rest of their experts' opinions. With respect to the substance of this argument, defendants addressed it in great detail in their opening brief and their opposition to plaintiffs' motion to exclude defendants' epidemiologists, and incorporate those discussions herein.[98] In brief, the top journals in the world continue to expect study authors to address statistical significance, and courts including the Third Circuit and this Court have rejected expert testimony that sought to ignore or minimize the importance of statistical significance. *See, e.g.*, *Zoloft III*, 858 F.3d at 793-94, 799;[99] *Bracco Diagnostics, Inc. v. Amersham Health, Inc.*, 627 F. Supp. 2d 384, 405-06, 452 (D.N.J. 2009) (Wolfson, J.) (holding that expert testimony that rejected "the 0.05 p-value test for

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98 (Defs.' Br. at 61-66; Defs.' Epi. Opp'n at 23-31.)

99 Plaintiffs' attempt to distinguish *Zoloft III* as "noise," falsely claiming that the case involved "no observational studies that demonstrated a statistically significant association." (Pls.' Opp'n at 106-08.) In fact, however, the expert in *Zoloft III* "presented five studies reporting a significant association," as more fully addressed in Defendants' Opposition to Plaintiffs' Motion to Exclude Defendants' Epidemiologists. 858 F.3d at 790-91. (Defs.' Epi. Opp'n at 26 n.69.) Moreover, plaintiffs ignore the Third Circuit's numerous statements about the value of testing for statistical significance. For example, plaintiffs' block quotation of the court's discussion of statistical significance conspicuously leaves out the rest of the paragraph highlighting the "importance" of statistical significance: "statistical significance . . . remains an important metric to distinguish between results supporting a true association and those resulting from mere chance." *Zoloft III*, 858 F.3d at 793. The court also expressly warned against "understat[ing]" the "importance" of statistical significance, *id.*, as plaintiffs attempt to do here.

statistical significance" was "not properly based upon science and [was] not reliable"; elsewhere observing that a meta-analysis was not "reliable [support] for the claim that" a product was safer than competitor products when "there was no statistically significant difference in" the incidence of disease and that "no reliable conclusions [could] be drawn from" a study that did not report a statistically significant difference).[100]

In addition, although some scientists have recently criticized the practice of placing dispositive weight on statistical significance,[101] that does not mean it was reliable for plaintiffs' experts to simply ignore statistical significance in their analyses. Indeed, none of the articles plaintiffs cite argues that non-statistically significant results that barely exceed 1.0 should be deemed consistent with a finding of causality. To the contrary, these authors explicitly did "***not advocat[e] for an anything goes situation, in which weak evidence suddenly becomes credible***."[102] But that is precisely what plaintiffs' experts did in deeming all of the

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100 *See also Joiner*, 522 U.S. at 145-47 (affirming exclusion of expert testimony that exposure to chemical caused cancer because expert relied on a study that reported an "increase, however, [that] was not statistically significant"); *Burst v. Shell Oil Co.*, 650 F. App'x 170, 174-75 (5th Cir. 2016) (per curiam) (affirming exclusion where expert relied on studies that "did not exhibit statistically significant results").

101 (*See* Pls.' Opp'n at 108-10.)

102 Amrhein et al., *Retire Statistical Significance*, 567 Nature 305, 306 (2019) (attached as Ex. A8 to Tersigni Cert.) (emphasis added).

talc studies consistent without regard for whether they were statistically significant or had divergent risk magnitudes.

Finally, plaintiffs' argument that "Professor Hill himself" criticized statistical significance is misleading because plaintiffs' quotation omits Hill's statement that testing for significance "***can, and, should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects***."[103] Hill's full statement is the opposite of an "admonition against 'significance testing,'"[104] and instead is a reminder of the central role it "can, and, should" play in a causation analysis.

In short, the notion that science has abandoned the longstanding practice of considering whether study results are statistically significant is false, and plaintiffs' experts' practice of ignoring statistical significance is unreliable.

C. Plaintiffs' Attempt To Redefine Dose Response Out Of The Bradford Hill Criteria Further Highlights The Unreliability Of Their Experts' Opinions.

As set forth in defendants' opening brief, plaintiffs' experts' dose-response opinions are all unreliable, albeit in different ways. Some experts acknowledge the evidence is equivocal but unreliably assert that ***any*** evidence of dose response

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103 Hill 1965 at 299 (emphasis added). (*See* Pls.' Opp'n at 112 (omitting these statements by use of an ellipsis).)

104 (*See id.*)

suffices;[105] some experts haphazardly assert that dose response can be disregarded in light of the alleged strength of the other Bradford Hill considerations;[106] and some experts offer various highly speculative claims about why stronger evidence of dose response is lacking.[107] In response, plaintiffs double down on the notion that "***any* evidence of *any* kind which would support a dose-response relationship"** suffices and then point to a smattering of studies that they claim are evidence of a dose-response relationship between talcum powder exposure and ovarian cancer.[108] As discussed below, plaintiffs' "any" dose-response argument misperceives this fundamental element of Bradford Hill and is at odds with the significant weight of the evidence that negates such a relationship with respect to talcum powder and ovarian cancer. And plaintiffs' reliance on a handful of studies that they believe contain evidence of a dose response only highlights their experts' failure to account for the broader talc data that do ***not*** show such a relationship.

First, plaintiffs argue that evidence of dose response is not required at all; or that in any event, Bradford Hill only requires "*any evidence* of dose response" –

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105 (Defs.' Br. at 68-70 & n.162 (identifying Drs. Kane, Singh, Smith-Bindman, Wolf, Saed and Siemiatycki as advancing such arguments).)

106 (*Id.* at 70 & n.164 (identifying Drs. Carson, Moorman, Smith-Bindman, Smith and Wolf as advancing such arguments).)

107 (*Id.* at 71-77 & n.166 (identifying Drs. Kane, McTiernan, Moorman, Singh and Plunkett as advancing such arguments).)

108 (Pls.' Opp'n at 156-65.)

without regard to what the "*body of data*" says on this score.[109] This argument is premised on a misreading of Bradford Hill. Plaintiffs highlight Hill's acknowledgment that it is often difficult to "'secure satisfactory quantitative measure of the environment which will permit us to explore this dose response.'"[110] But as other passages in the same block quotation indicate, Hill also admonished scientists to "look most carefully for such evidence" and "invariably seek it."[111] It follows perforce that where, as here, evidence addressing dose response exists, a scientist is not free to ignore it and proceed to a causal conclusion without assessing it. Indeed, several cases have recognized that a "dose-response relationship is a key element of reliability in toxic tort cases." *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1241 n.6, 1242 (11th Cir. 2005).[112] And plaintiffs' own expert Dr. Siemiatycki recognized in his report that

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109 (*Id.* at 156-57.)

110 (*Id.* (quoting Hill 1965 at 298) (emphasis omitted).)

111 Hill 1965 at 298.

112 (*See also* Defs.' Br. at 67-68 (collecting additional authority).) Plaintiffs do not dispute *McClain's* observation, instead citing it for the proposition that dose-response data need not yield "precise numbers" (Pls.' Opp'n at 159); but defendants have not argued that such precision is required. And plaintiffs conspicuously omit the very next sentence of *McClain*, which states that "the link between an expert's opinions and the dose-response relationship is a key element of reliability in toxic tort cases." 401 F.3d at 1241 n.6; *see also id.* at 1240 (excluding expert for "neglecting the hallmark of the science of toxic torts – the dose-response relationship").

"[a]n ***important*** part of the evaluation of causality is to determine whether the results display any kind of dose-response pattern."[113]

By the same token, it is also incorrect that "any evidence [of dose response] of any kind" may furnish a reliable basis for an expert to conclude that dose response supports a causal conclusion. The implication of this assertion is that experts are free to trumpet positive data and ignore negative studies without

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[113] (Siemiatycki Rep. at 42 (emphasis added).) Plaintiffs' cases at most indicate that there are some instances in which the evidence regarding dose response may be non-existent or too attenuated to weigh in favor of, or against, a causal inference. *See, e.g.*, *In re Avandia Mktg., Sales Practices & Prods. Liab. Litig.*, No. 2007-MD-1871, 2011 WL 13576, at *9, *14 (E.D. Pa. Jan. 4, 2011) (causation testimony that did not consider dose response was admissible "because there was little variation in the prescribed doses" of the drug, and dose response accordingly "could not [be] assess[ed]"); *In re Zicam Cold Remedy Mktg., Sales Practices, & Prods. Liab. Litig.*, 797 F. Supp. 2d 940, 943, 946 (D. Ariz. 2011) (stating that "[g]iven the challenge of determining a toxic dose," "plaintiffs need not prove a toxic dosage of Zicam," but instead "must demonstrate Zicam 'is toxic to humans given substantial exposure'") (citation omitted). The Reference Manual and "textbooks" plaintiffs rely on are also inapposite because they do not address situations like the one here where studies have been all over the place in terms of dose response. (Pls.' Opp'n at 158.) *See, e.g.*, Epidemiology Reference Manual at 603 (explaining that "some causal agents do not exhibit a dose-response relationship," "[t]hus, a dose-response relationship is strong, but not essential, evidence that the relationship between an agent and disease is causal"); Gordis, *Epidemiology* at 251(5th ed. 2013) (cited in Pls.' Opp'n) (explaining that "[i]n some cases in which a threshold may exist," "the absence of a dose-response relationship does not necessarily rule out a causal relationship"). Finally, plaintiffs additionally cite cases that do not address the dose-response requirement and thus do not support their arguments. *See Fosamax*, 645 F. Supp. 2d at 188; *In re Neurontin Mktg., Sales Practices & Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 159 n.72 (D. Mass. 2009); *Bartlett v. Mut. Pharm. Co.*, 759 F. Supp. 2d 171 (D.N.H. 2010) (including no discussion of dose response or the Bradford Hill analysis).

attempting to reconcile them. Such slanted accounting is unscientific and has been rejected by courts. *See In re Mirena*, 341 F. Supp. 3d at 289 (rejecting an expert's suggestion of "a dose-response relationship between LNG and IIH" where that expert "ignore[d] contrary data about contraceptives that use LNG in much higher doses . . . which [the expert] acknowledge[d] d[id] not cause IIH").[114] This is so because, as with any reliable scientific methodology, it is essential to account for conflicting data, and plaintiffs' experts did not do so.[115]

Second, plaintiffs also highlight isolated studies and meta-analyses that they believe contain evidence of a dose response supporting their experts' opinions on the subject.[116] This approach fails for the reasons just explained: plaintiffs' experts must not only identify "any evidence" of dose response but ***all*** of it, and then reconcile the positive, neutral and negative studies. They have not done so –

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[114] *See also In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d 1345, 1353 (S.D. Fla. 2011) (requiring "dose-response evidence which [p]laintiffs' experts may use to reliably infer what type of exposure level to [the product] is necessary to induce [injury]"); *Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 188 (E.D.N.Y. 2001) (excluding general causation expert who cited literature in which "[f]ew, if any, dose-response relationships were reported"), *aff'd*, 303 F.3d 256 (2d Cir. 2002).

[115] (*See, e.g.*, Plunkett Rep. at 50 (finding "sufficient scientific data supporting the existence of a dose-response relationship" based on "several human studies"); McTiernan Rep. at 65-66 (placing "significant weight" on dose response despite acknowledging mixed results in overall body of studies); Singh Rep. at 65 (finding dose response "compelling of my causation analysis" based on "[s]everal studies").)

[116] (Pls.' Opp'n at 160-63.)

an omission that renders their causation opinions unreliable because the total body of evidence on dose response contradicts such a finding.[117]

In any event, the publications plaintiffs do identify fail to support their experts' opinions:

Terry 2013. With respect to Terry 2013, plaintiffs do not acknowledge that the authors themselves disagreed with plaintiffs' experts' conclusions about a dose-response relationship; according to the paper, their data showed "***no significant trend in risk (P=0.17) with increasing number of lifetime applications***."[118] Plaintiffs' omission is remarkable considering that plaintiffs' experts deem this study "'by far the most important evidence on dose response.'"[119]

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[117] (*See* Defs.' Br. at 68 n.161 (collecting authority synthesizing the literature); Merlo Rep. at 45 ("Almost every epidemiological study has failed to show any dose-response relationship[.]"); Diette Rep. at 27 ("[O]verall, the literature is very inconsistent with regard to dose-response, as Drs. Smith-Bindman and Moorman concede"; further noting none of the cohort studies and only a handful of case-control studies purport to have found a dose response); Expert Report of Karla Ballman, Ph.D. ("Ballman Rep.") at 30-32 & tbls. 1 & 2, Feb. 25, 2019 (attached as Ex. C25 to Tersigni Cert.) (summarizing dose-response findings from various studies, very few of which reported a dose response).)

[118] Terry et al., *Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls*, 6(8) Cancer Prevention Res. 811, 811 (abstract) (2013) ("Terry 2013") (attached as Ex. A139 to Tersigni Cert.) (emphasis added). .

[119] (Pls.' Opp'n at 163 n.436 (quoting Dep. of Jack Siemiatycki, Ph.D. ("Siemiatycki Dep.") 122:22-123:7, Jan. 31, 2019 (attached as Ex. B29 to Tersigni

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Moreover, to the extent data from Terry 2013 indicate any dose response at all, it is only when non-talc users are included, which is not an appropriate way to calculate dose response.[120] As Drs. Ballman and Merlo explain in their reports, including nonusers makes the analysis redundant with measuring the effect of ever versus never use (i.e., strength of association).[121] It also creates a risk of false positives because factors potentially creating a spurious association could likewise be "driving the dose-relationship results."[122] Accordingly, as Dr. Ballman explains, "[o]nce ever use versus never use has been established as an association, to tease out the effects of the amount of use, the analysis needs to be done only in

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Cert.)); *see also, e.g.*, McTiernan Rep. at 55, 65 (claiming that Terry 2013 "provides strong evidence" of causation in part because "the dose-response effect was clear"; later finding dose response satisfied "particularly" based on Terry 2013); Kane Rep. at 18 (Terry 2013 "provide[s] clear evidence of a dose effect").) The quote plaintiffs use from Dr. Siemiatycki is telling. Even when factoring in what he deems "'powerful'" dose-response evidence, the most Dr. Siemiatycki is able to say is that "'the data are certainly compatible with the notion of a dose-response relationship'" and "'tend to indicate dose-response relationship.'" (*See id.*)

120 The purported finding of dose response when non-users were included was limited to non-mucinous ovarian cancer cases. *See* Terry 2013 at 817.

121 (Defs.' Br. at 74 (citing Ballman Rep.); Merlo Rep. at 32-35.)

122 (Ballman Rep. at 30 (explaining that excluding nonusers "ensure[s] that the inherent residual confounding and bias that exist in case-control studies is not driving the dose-relationship results. If the dose-response relationship is seen in just the users of talcum powder products, it is less likely that there was substantial recall bias in the association between ever use and never use.").)

individuals who were exposed . . . to determine whether there is a dose-response relationship: i.e., whether higher exposure results in a stronger association."[123] Indeed, that is precisely what the Terry authors concluded about their own data. As they explained, "[t]aken together," the fact that a trend was established when non-users were included but not when they were excluded "suggest[s] that the significant trend test largely reflects the comparison of ever-regular use with never use" – i.e., the underlying association, not a true dose response.[124] Plaintiffs do not address this fact.[125] And while they broadly contend that it is appropriate to

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[123] (Ballman Rep. at 30.) The Terry authors' conclusion that their study did not show a dose response reflects that unexposed women should not be included. Thus, although Dr. Siemiatycki has stated that "the investigators of the original studies . . . chose which would be the 'best' result to represent the study, and this . . . is more reliable than outside authors making that decision" (Siemiatycki Rep. at 41), his analysis of the Terry study violates this principle. Dr. Ballman additionally explains that several other studies plaintiffs' experts rely on also indicate a dose response only when including nonusers. (Ballman Rep. at 29 ("The reported p-values for the Wu, Cramer and Schildkraut results include women with no perineal/genital talcum powder exposure, which means they may only be significant because of the observed association between ever use and never use . . . .").)

[124] Terry 2013 at 817.

[125] Nor generally do plaintiffs' experts. (*See* McTiernan Rep. at 54-55 (omitting this conclusion from lengthy discussion of Terry 2013); Siemiatycki Rep. at 43-45 (similar); *see also* Kane Rep. at 35; Plunkett Rep. at 50 (both relying on Terry 2013 as evidence of dose response but ignoring the authors' statement that their data reflected an association for ever use, not a dose response).) Dr. Moorman (who did not heavily weigh dose response in favor of causation) acknowledges this conclusion in her discussion of Terry 2013. (Moorman Rep. at

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include non-users in evaluations of dose response,[126] plaintiffs ignore that their own expert, Dr. Siemiatycki, agreed with defendants – at least before he changed his opinion for this litigation, which "seriously undermines the reliability of" his methodology. *Fireman's Fund Ins. Co. v. Canon U.S.A., Inc.*, 394 F.3d 1054, 1059 (8th Cir. 2005).[127]

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31.) In her discussion, Moorman contends that the Terry data suggest that "the dose-response relationship may not be a simple linear trend," but this theory is speculative, as explained in defendants' opening brief (Defs.' Br. at 76-77), which is another issue plaintiffs fail to address.

[126] (Pls.' Opp'n at 162-63.) Plaintiffs cite two articles in arguing that the unexposed category should be included. (Pls.' Opp'n at 163 n.435.) The first, by plaintiffs' expert Sander Greenland, stands only for the proposition that "deletion of the unexposed (zero-exposed) is not ***always*** the best approach," under certain circumstances. *See* Greenland, *Dose-Response and Trend Analysis in Epidemiology: Alternatives to Categorical Analysis Epidemiology*, 6 Epidemiol. 356, 362 (1995) (attached as Ex. 154 to Pls.' Opp'n) (cited in Pls.' Opp'n at 163 n.435) (emphasis added). This article also recognizes that dose response can be "influenced by the unexposed." *Id.* at 362. The second article focused on a different issue and did not provide any support for its statement that "[i]n exposure studies, an unexposed group . . . is commonly compared with several exposure groups." Horthorn et al., *Trend tests for the evaluation of exposure-response relationships in epidemiological exposure studies*, Epidemiologic Perspectives & Innovations 1, 1 (2009) (attached as Ex. 153 to Pls.' Opp'n).

[127] (Defs.' Br. at 74-75 (explaining that Dr. Siemiatycki wrote in a report for a different talc case that "the appropriate statistical test for [dose] trend is one that ***excludes*** the baseline unexposed category (since the baseline category is used for the overall binary RR estimate, and it is preferable to keep the trend test independent of the test for overall RR)"); *see also* Dep. of Jack Siemiatycki, Ph.D. 334:17-345:6, 347:18-348:16, *Oules v. Johnson & Johnson*, No. 2014 CA 088327

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Taher 2018. Relying on the unpublished Taher 2018 meta-analysis, plaintiffs assert that "evidence of dose response . . . observed by the PSC's experts has also been observed by scientists *outside* of the litigation context."[128] However, Taher expressly acknowledges that the dose-response evidence consists of "[c]onflicting findings."[129] To the extent Taher's statement that the data supported a "possible increasing trend" in risk[130] is viewed as an endorsement of dose response, his opinions are at odds with the scientific and regulatory communities. The FDA, IARC and the National Cancer Institute have all found dose-response evidence "lacking" or unsubstantiated.[131] And even the Health Canada Draft

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B (D.C. Super. Ct. Dec. 16, 2016) (explaining he "favor[s] excluding the nonusers" because "the trend test should be kept separate from the ever never result").)

128 (Pls.' Opp'n at 164.)

129 Taher 2018 at 37.

130 *Id.* at 38.

131 FDA Denial Letter at 4 ("dose-response evidence is lacking"); Nat'l Cancer Inst., *Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)–Health Professional Version*, https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq (last updated Mar. 1, 2019) ("2019 NCI PDQ") (attached as Ex. A104 to Tersigni Cert.) (reporting that "a dose response relationship was not found" and "there was no increased risk observed for increasing duration of use"); IARC 2010 Monograph at 412 ("inconsistent" evidence of a dose response); *see also* Langseth 2008 at 359 (summary of IARC review co-authored by Dr. Siemiatycki explaining that a crucial missing piece of causation evidence was "***the absence of clear exposure response associations in most studies***") (emphasis added).

Screening Assessment – which itself relied heavily on Taher – states that ***no*** studies "demonstrate[ ] both a clear dose-response trend and statistical significance."[132] In short, plaintiffs' tepid appeal to "outside" scientists only confirms the unreliability of their experts' dose-response opinions.

Finally, although plaintiffs also briefly reference a few other meta-analyses and studies, these studies do not support plaintiffs' experts' opinions on dose response either.[133] For example, plaintiffs point to data in the 2018 meta-analyses by Berge and Penninkilampi as supposedly "support[ing] the presence of a dose-response relationship."[134] But plaintiffs ignore that the Berge authors cautioned that "the modest association between both duration and frequency of use of talc may reflect a true relationship, or recall bias or confounding," since their data pool "was not very large" and "analyses based on larger datasets would be required."[135] And the Penninkilampi meta-analysis found a "slightly greater increased risk of ovarian cancer with" greater than 3,600 lifetime talc applications compared with those with fewer than 3,600 lifetime applications, but it did not characterize this

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132 Draft Screening Assessment at 20-21 (emphasis added).

133 (Pls.' Opp'n at 161; *see also*, *e.g.*, Plunkett Rep. at 50; Kane Rep. at 35; Singh Rep. at 65; Siemiatycki Rep. at 68 (all relying on Berge 2018 and/or Penninkilampi 2018).)

134 (Pls.' Opp'n at 161.)

135 Berge 2018 at 254.

finding as a "dose response," and the paper does not indicate that any statistical comparison was attempted.[136] Moreover, as defendants' experts have explained, this was an "arbitrary dichotomous categorization of lifetime use," and any number of different demarcation points might have produced a different result.[137] Lastly, plaintiffs (like their experts)[138] also point to the Cramer 2016 study;[139] but ***both*** sides' experts have recognized that Cramer identified "no clear pattern suggesting a dose-response effect."[140]

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136 *See* Penninkilampi 2018 at 45.

137 (*See, e.g.*, Diette Rep. at 29.) This same uninformative technique was used in Schildkraut 2016, which plaintiffs and their experts also cite. (Pls.' Opp'n at 161; *see also, e.g.*, Singh Rep. at 65; Plunkett Rep. at 50.)

138 (*See, e.g.*, Expert Report of Daniel L. Clarke-Pearson, M.D. ("Clarke-Pearson Rep.") at 6, Nov. 16, 2018 (attached as Ex. C14 to Tersigni Cert.); Expert Report of Judith Wolf, M.D. ("Wolf Rep.") at 7, Nov. 16, 2018 (attached as Ex. C23 to Tersigni Cert.); McTiernan Rep. at 32; Plunkett Rep. at 50.)

139 (Pls.' Opp'n at 161.)

140 (Merlo Rep. at 24, 32 (discussing Cramer 2016 at 336-37 tbl. 1); Clarke-Pearson Dep. 192:12-14 (admitting "[t]here is not a consistent dose response" in Cramer 2016); Expert Report of Cheryl Christine Saenz, M.D. at 10, 26-27, Feb. 25, 2019 (attached as C12 to Tersigni Cert.) (explaining that the Cramer 2016 dose-response "data was sinusoidal").) Cramer's dose-response data are in any event unreliable because he did not adjust for several ovarian risk factors in the dose-response table that he did adjust for in other tables. *See generally* Cramer 2016. Plaintiffs also make very brief reference to studies by Wu, Whittemore and Rosenblatt (Pls.' Opp'n at 162), but they do not explain how these isolated findings support their experts' conclusions that dose response is established in light of the entire body of evidence; and in any event, neither Whittemore nor Rosenblatt actually claimed to have established statistically significant trends.

For this reason, too, plaintiffs' effort to argue that their experts' dose-response opinions were reliable should be rejected.

D. Plaintiffs' Discussion Of The Other Bradford Hill Factors Demonstrates That Their Experts Did Not Reliably Consider Them.

As demonstrated in defendants' opening brief, plaintiffs' experts' limited opinions with respect to the biological plausibility, specificity, coherence, analogy, experiment and temporality considerations also do not reliably support a causal inference.[141] Plaintiffs' arguments in response are, once again, meritless.

Biological Plausibility. As set forth in detail in defendants' opening brief and their Biological Plausibility *Daubert* Motion, plaintiffs' experts' causation theory also fails because they lack a reliable scientific basis to conclude that there is a ***plausible*** mechanism by which talc can cause ovarian cancer. In response, plaintiffs argue that defendants have misstated the standard for establishing biological plausibility by demanding that it be "proven" to a "certainty" – and that their experts have identified reliable evidence that talc migrates to the ovaries, produces cancer-causing inflammation there, and also contains other known carcinogens. As set forth below, and in more detail in Defendants' Reply In

[141] (Defs.' Br. at 78-94.)

Support Of Motion To Exclude Plaintiffs' Experts' Opinions Related To Biological Plausibility, which is incorporated herein, all of these arguments fail.

First, contrary to plaintiffs' suggestion, defendants have never argued that plaintiffs' experts must "prove" a biological mechanism by which talc causes cancer to a "certainty."[142] Instead, defendants have explained, consistent with the relevant law, that courts reject biological plausibility theories that are "merely . . . unproven hypothes[e]s" unsupported by "evidence of [how] the mechanism . . . works." *In re Accutane Prods. Liab.*, 511 F. Supp. 2d 1288, 1295 (M.D. Fla. 2007); *see also, e.g., Soldo v. Sandoz Pharm. Corp.*, No. 98-1712, 2003 WL 22005007, at *4 (W.D. Pa. Jan. 1, 2003) (a "proposed mechanism" must be "substantiated by scientific evidence").[143] In addition, courts have recognized that where, as here, there is only weak or equivocal epidemiological evidence of an association between an agent and disease, "it is not enough" "for a general causation expert to opine that a biological pathway exists but is not well understood." *In re Mirena*,

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142 (Pls.' Opp'n at 165-70.)

143 *See also In re Propulsid Prods. Liab. Litig.*, 261 F. Supp. 2d 603, 616 (E.D. La. 2003) (excluding experts who "have left too great a gap in their theory of biologic plausibility to support their arguments"); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 473 (E.D. Pa. 2014) (explaining that an expert opining on biological plausibility may not "testify to an untested hypothesis," and instead must invoke biological pathways with a "well established effect") (citation omitted).

341 F. Supp. 3d at 286. In other words, biological plausibility takes on heightened importance where, as here, a subset of studies only show a weak association.[144]

Plaintiffs' own authorities are not to the contrary, noting that "an analysis of biological plausibility 'asks whether the hypothesized causal link is ***credible in light of what is known from science and medicine about the human body*** and the potentially offending agent.'" *In re Testosterone*, 2017 WL 1833173, at *11 (citation omitted); *see also In re Abilify*, 299 F. Supp. 3d at 1343-44 (only admitting those biological plausibility opinions for which "[e]ach element of th[e] proposed mechanism of action [was] adequately supported by peer-reviewed, published scientific literature and sound scientific reasoning" and rejecting others that "present[ed] an extrapolation problem" because they were not supported by relevant science). The Reference Manual, which plaintiffs also cite, similarly notes that for a theory of biological plausibility, an "observation should be confirmed" with evidence "before significance is attached to it."[145]

As defendants explained in their opening brief, there simply is no reliable scientific evidence supporting plaintiffs' hypothesis regarding the mechanism by which talc is purportedly capable of causing ovarian cancer. Indeed, Judge

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144 *See also* Wynder 1982 at 465; Epidemiology Reference Manual at 602 (explaining that "epidemiologist[s] will scrutinize [weak] associations more closely").

145 Epidemiology Reference Manual at 604-05.

Johnson rejected nearly identical general causation expert opinions in *Carl*, finding that the experts "fail[ed] to provide a coherent explanation to support their hypothesis for biologic plausibility." 2016 WL 4580145, at *12. The *Carl* decision considered and rejected essentially the same biological plausibility theories plaintiffs' experts propose here – i.e., that talc migrates to the ovaries, where it causes cancer by triggering inflammation and oxidative stress. Yet, plaintiffs essentially ignore that decision – including Judge Johnson's observation that it is "universally accepted that mutations in critical genes is the mechanism that causes cancer, and talc doesn't cause mutations." *Id.* at *14.[146]

Second, while plaintiffs argue that there is "biologic" evidence supporting their experts' hypotheses that externally-applied talc can migrate upwards into the genital tract, reach the ovaries (or fallopian tubes) and cause chronic inflammation triggering ovarian cancer, they simply are not able to point to any reliable science demonstrating that this is the case.

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[146] Elsewhere in their brief, plaintiffs argue that Judge Johnson's ruling should be ignored because there is "no overlap" on their expert roster and "the scientific landscape has evolved significantly" since that decision. (Pls.' Opp'n at 67-68.) The first argument is not credible since plaintiffs' experts offer nearly identical theories and methodologies to those that were before the court in *Carl*. The second is also baseless. Plaintiffs would have the Court believe that there has been a sea change in the evidentiary landscape based solely on the publication of two meta-analyses and the Draft Screening Assessment. These publications do not support plaintiffs' arguments, as explained throughout this brief, and in any event, they contributed ***no new primary data***.

For example, plaintiffs insist that "government agencies and their employees have noted that both migration and inhalation are *plausible* . . . mechanisms" by which externally-applied talc is capable of making its way up through the entire genital tract and to the ovaries.[147] But plaintiffs misrepresent these agencies' ultimate findings. Most notably, plaintiffs cite the FDA, but ignore that it ultimately concluded that "[a] cogent biological mechanism by which talc might lead to ovarian cancer ***is lacking***."[148] Similarly, plaintiffs cite IARC, but omit its conclusion that "the evidence for retrograde transport of talc to the ovaries in normal women is ***weak***" and that animal studies "showed ***no evidence*** of retrograde transport of talc to the ovaries."[149] And Health Canada, on which plaintiffs heavily rely, has merely acknowledged that it is "***hypothesized*** [that talc] . . . migrate[s] into the pelvis and ovarian tissue, causing irritation and

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147 (Pls.' Opp'n at 171-72.)

148 FDA Denial Letter at 4 (emphasis added) (discussed in Pls.' Opp'n at 171). As defendants have explained, the FDA's discrete conclusion on migration did not cite particular evidence and thus is impossible to evaluate. Elsewhere in their brief, plaintiffs tout the FDA's ban on powdered gloves as supposed evidence that talc causes inflammation (Pls.' Opp'n at 47-48), but this is highly misleading. The ban was actually of cornstarch due to ***its*** inflammatory properties. The FDA's Final Rule and the CFR provisions do not mention talc. *See*, *e.g.*, Banned Devices; Powdered Surgeon's Gloves, Powdered Patient Examination Gloves, and Absorbable Powder for Lubricating a Surgeon's Glove, 81 Fed. Reg. 91,722, 91,723-31 (Dec. 19, 2016) (attached as Ex. 82 to Pls.' Opp'n); 21 C.F.R. § 878.4460 (2017).

149 *See* IARC 2010 Monograph at 411 (emphases added).

inflammation,"[150] without identifying reliable science indicating that this is the case.

Plaintiffs also insist that "epidemiologists and regulatory agencies" provide "credible evidence that Talcum Powder Products (and its constituents) can provoke an inflammatory response and induce oxidative stress" that leads to ovarian cancer.[151] But epidemiological findings cannot serve as evidence of a biologically plausible ***mechanism*** by which talc actually triggers ovarian cancer in the real world. Further, while plaintiffs rely on the FDA and Health Canada as reliable evidence that talc causes chronic inflammation that causes ovarian cancer, they do not support that point. To the contrary, Health Canada has expressly noted that "the specific mechanism(s) and cascade of molecular events by which talc ***might*** cause ovarian cancer ***have not been identified***."[152] And, as set forth above, the FDA concluded that a "cogent biological mechanism by which talc might lead to ovarian cancer ***is lacking***."[153]

Third, plaintiffs' argument that the alleged presence of "asbestos, fibrous talc, nickel, chromium and cobalt" in the Products is sufficient evidence of

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150 Draft Screening Assessment at 21 (emphasis added).

151 (Pls.' Opp'n at 173.)

152 Draft Screening Assessment at 21 (emphases added).

153 FDA Denial Letter at 4 (emphasis added).

biological plausibility[154] also fails. As set forth in detail in defendants' briefing in support of their motions to exclude plaintiffs' experts' opinions regarding the alleged presence of asbestos, heavy metals and fibrous talc in the Products, plaintiffs lack any reliable evidence that the Products contain such materials or that they are capable of causing ovarian cancer.[155]

Further, plaintiffs' own experts only purport to have identified a miniscule amount of asbestos in samples of the Products, in the range of 3.3 millionths of a percent.[156] As explained by Dr. Nadia Moore, the only expert in this litigation who has analyzed the amount of asbestos exposure that would result if plaintiffs' experts' findings were reliable, the cumulative lifetime exposure to the level of asbestos plaintiffs claim is present in the Products is at least 4,000 times below the

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154 (Pls.' Opp'n at 174-78.)

155 (*See* Defs.' Mem. of Law in Supp. of Mot. to Exclude Pls.' Experts' Asbestos-Related Ops. ("Defs.' Asbestos Mot.") at 26-37, 81-93, May 7, 2019 (ECF No. 9736-3); Defs.' Mem. of Law in Supp. of Mot. to Exclude Pls.' Experts' Ops. Regarding Heavy Metals & Fragrances in Johnson's Baby Powder and Shower to Shower at 17-37, 43-48, May 7, 2019 (ECF No. 9736-4); Defs.' Mem. of Law in Supp. of Mot. To Exclude Pls.' Experts' Ops. Regarding Biological Plausibility ("Defs.' Biological Plausibility Mot.") at 47-69, May 7, 2019 (ECF No. 9736-1).)

156 (Defs.' Asbestos Mot. at 3.)

Occupational Safety and Health Administration's ("OSHA") permissible lifetime exposure limit.[157]

There is also no truth to plaintiffs' assertion that defendants' "prior external consultants" – namely Drs. Huncharek and Muscat – have admitted that asbestos is present in talc and provides a "biologically plausible explanation" for how talc causes cancer.[158] As defendants have explained in other briefing, while Drs. Huncharek and Muscat have generally recognized that the presence of asbestos in the Products "could possibly represent a carcinogenic risk," they did not in any way conclude that there is a connection between asbestos exposure at the levels alleged by plaintiffs here and ovarian cancer.[159] Moreover, Drs. Huncharek and Muscat concluded that the epidemiological evidence did ***not*** support a causal relationship between the use of talc and ovarian cancer.[160]

In short, plaintiffs' experts lack a reliable scientific basis for any of the links in the chain of their complex hypothesis that externally-applied talc can enter the body, travel upward through the genital tract, reach a woman's ovaries (or

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157 (*Id*. at 85 (citing Expert Report of H. Nadia Moore, Ph.D., D.A.B.T., E.R.T. at 52-56, Feb. 25, 2019 (attached as Ex. C19 to Tersigni Cert.)).)

158 (Pls.' Opp'n at 174-75.)

159 (*See* Defs.' Reply in Supp. of Mot. to Exclude Pls.' Experts' Asbestos-Related Ops. at 52 n.136 (filed herewith and incorporated herein).)

160 (*Id*.)

fallopian tubes) and trigger chronic inflammation that then instigates ovarian cancer. Accordingly, biological plausibility is lacking.

Specificity. As noted in defendants' opening brief, plaintiffs' experts place little weight on specificity. This is presumably because the specificity consideration further illustrates the unreliability of their opinions. After all, plaintiffs' experts posit that external talc use can cause not just one disease, but rather all subtypes of epithelial ovarian cancer – making their theory highly ***unspecific***.[161]

In response, plaintiffs argue that there is specificity of association because talc has been associated with ovarian cancers and not cancers of other tissues or organs, and that there is evidence that talc is more strongly associated with serous ovarian cancer specifically.[162] These arguments lack merit. The first repeats the errors of plaintiffs' experts by treating epithelial ovarian cancers as a homogenous

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161 (Defs.' Br. at 82-84.)

162 (Pls.' Opp'n at 179-81.) In reality, a number of plaintiffs have more than "suggest[ed]" an association between talc and other organs in the numerous lawsuits alleging that talc use causes mesothelioma and lung cancer. Defendants agree that the science does not support these allegations, as plaintiffs' argument implicitly concedes.

disease entity when, as already explained, they have different etiologies and causes, making it highly improbable that talc could cause all of them.[163]

Plaintiffs' attempt to shore up their experts' treatment of specificity by emphasizing serous ovarian cancer has a significant problem: most of plaintiffs' experts' opinions do not embrace this distinction. Plaintiffs' experts' opinions must stand on their own logic – not logic offered post hoc by plaintiffs' counsel. *Tamraz*, 620 F.3d at 672-73 (the expert's "opinion cannot escape its own logic"). And while Dr. Smith-Bindman did separately examine HGSOC, she did not limit her causation opinion to it, instead opining like the rest of plaintiffs' experts that external talc use can cause epithelial ovarian cancer generally.[164] Accordingly, no plaintiffs' expert has reliably opined on specificity.

Coherence. Plaintiffs' experts have also failed to reliably conclude that coherence is satisfied, for several reasons explained in defendants' opening brief: the notion that a single exposure could cause multiple cancers with different

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163 (*See, e.g.*, Defs.' Biological Plausibility Mot. at 9-18 (detailing these differences); Neel Rep. at 13-14 (same).)

164 (*See* Dep. of Rebecca Smith-Bindman, M.D. Vol. II 323:3-19, Feb. 8, 2019 (attached as Ex. B42 to Tersigni Cert.) (explaining that while her more "limited review . . . focused on serous cancer," she looked at "all ovarian cancer – epithelial ovarian cancer"); *see also, e.g.*, Smith-Bindman Rep. at 4 ("In my expert opinion, regular exposure to talcum powder products causes ovarian cancer").) In any event, as elaborated in Part III, below, Dr. Smith-Bindman's HGSOC-specific meta-analysis is itself unreliable.

etiologies is not coherent with present medical knowledge; there are no data that talc causes genetic mutations – the accepted origin of all ovarian cancers; animal data have never borne out the theory that talc could be carcinogenic; studies of talc-dusted diaphragms and condoms do not show elevated risk, which is counterintuitive because these applications would place talc more proximally to the ovaries; and talc does not cause other gynecologic cancers, a fact in tension with the concept espoused by plaintiffs' experts that talc could cause a broad range of ovarian cancers.[165]

Plaintiffs do not respond to ***any*** of these serious problems with their experts' conclusions. Instead, plaintiffs contend that their experts' causation theory is coherent based on the "observational studies" and "biologic evidence," rehashing the same arguments that defendants have already demonstrated do not support plaintiffs' experts' unreliable treatment of the other Bradford Hill factors.[166] Indeed, the only specific argument plaintiffs press with respect to coherence is that there is "evidence" that tubal ligation reduces ovarian cancer risk in talc users.[167] But the data on the effect of tubal ligation among talc users are highly

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165 (Defs.' Br. at 84-88.)

166 (Pls.' Opp'n at 186.)

167 (*Id.*)

inconsistent,[168] and as a general matter, recent research suggests that the mechanism by which tubal ligation may reduce ovarian cancer risk is that it cuts off exposure of the fallopian tubes to follicular fluid from the ovaries.[169] This explanation is itself more coherent with what is now understood about HGSOC – i.e., that it is thought to originate in the fallopian tubes,[170] as even plaintiffs' experts' acknowledge.[171] Not a single one of plaintiffs' experts addressed this explanation for the apparently risk-reducing effect of tubal ligation on ovarian cancer in his or her report even though it has been discussed in the published literature.

Analogy. As set forth in defendants' opening brief, plaintiffs' experts do not reliably opine on the analogy factor, either, because the only analogy they posit is to asbestos, and that analogy lacks a reliable basis. In a nutshell: talc's characteristics differ from those of asbestos; talc, unlike asbestos, has not been linked to mesothelioma; and mesothelioma is a very distinct disease from ovarian

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168 (Diette Rep. at 39.)

169 (*E.g.*, Expert Report of Ie-Ming Shih, M.D., Ph.D. at 16, Feb. 25, 2019 (attached as Ex. C20 to Tersigni Cert.) (citing literature).)

170 (*Id.* at 10-11.)

171 (*E.g.*, Dep. of Ghassan Saed, Ph.D. Vol. 1 169:14-16, Jan. 23, 2019 (attached as Ex. B12 to Tersigni Cert.) (testifying that "there are many studies now indicating that the source of epithelial ovarian cancer come from fallopian tube").)

cancer.[172] Plaintiffs' response is all of two sentences and does nothing more than repeat that plaintiffs' experts have analogized to asbestos – ignoring all of the serious problems with this analogy that render plaintiffs' experts' dependence on it entirely unreliable.[173]

Experiment. As explained in defendants' opening brief, plaintiffs' experts either: (1) take the position that the experiment factor is irrelevant because clinical trials cannot be conducted; or (2) assert that in vitro and animal studies support a causal conclusion, an assertion that lacks a reliable basis since these studies have failed to demonstrate a carcinogenic effect of talc.[174] Plaintiffs' response essentially concedes that this factor is at best neutral.[175] This concession does not go far enough, especially because studies show that animals exposed to huge doses of talc do not develop ovarian cancer.[176]

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172 (Defs.' Br. at 88-92 & n.212 (identifying opinions from Dr. Clarke-Pearson, Kane, Smith-Bindman, Siemiatycki and Smith as proposing an analogy to asbestos).)

173 (Pls.' Opp'n at 187.)

174 (Defs.' Br. at 92-93 & nn.223-25 (identifying Drs. McTiernan and Singh as acknowledging no clinical trials; Dr. Siemiatycki as ignoring the factor; and Drs. Smith-Bindman, Smith and Kane as relying on animal and in vitro studies).)

175 (*See* Pls.' Opp'n at 185 (agreeing with defendants that there have been no clinical trials).)

176 (*See generally* Defs.' Biological Plausibility Mot.)

Temporality. Defendants' opening brief explained that this factor is necessary but not sufficient for causation and that plaintiffs' experts thus placed outsized importance on it.[177] *See, e.g.*, *Buzzerd v. Flagship Carwash of Port St. Lucie, Inc.*, 669 F. Supp. 2d 514, 530 (M.D. Pa. 2009) ("[T]emporal connection standing alone is entitled to little weight in determining causation.") (citations omitted), *aff'd*, 397 F. App'x 797 (3d Cir. 2010). Plaintiffs do not respond. Instead, plaintiffs argue that the cohort studies insufficiently accounted for latency.[178] But even if there is a 20-to-30-year latency period for ovarian cancer as plaintiffs continue to speculate in their opposition brief,[179] the cohort study participants likely began using talc long before the studies began.[180] Indeed, as defendants have previously argued, the available data suggest that most women start using talc in their 20s, the mean duration of use is greater than 20 years, and the average age of women at the end of each cohort study was over 50.[181] As

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177 (Defs.' Br. at 93-94 & n.226 (identifying statements from plaintiffs' experts Drs. McTiernan, Smith-Bindman and Singh to the effect that temporality was a "significant" factor for them).)

178 (*See* Pls.' Opp'n at 184.)

179 (*Id.*)

180 (*See* Merlo Rep. at 38-39 ("the women followed in all of these studies presumably did not start using talc for the first time the day the studies began and therefore would have had longer durations of use than the time period of the study – ***in most cases many years more***") (emphasis added).)

181 (Defs.' Br. at 55-56.)

discussed in defendants' opening brief, these facts, coupled with the studies' extensive follow-up periods, renders the latency theory speculative and erroneous.[182]

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In sum, plaintiffs' opposition brief fails to demonstrate that plaintiffs' experts reliably applied the Bradford Hill framework. Indeed, the very organization of plaintiffs' brief – which places so much emphasis on consistency and dwindling attention to the remaining considerations – indicates that not even plaintiffs believe that their experts seriously (much less reliably) applied the other fundamental factors in the Bradford Hill framework. In short, plaintiffs' own brief confirms that plaintiffs' experts selectively and unscientifically engaged with the Bradford Hill factors, as opposed to methodically tethering their sweeping causal theories to each of these important elements. Such an approach flouts Bradford Hill and underscores the unreliability of plaintiffs' experts' causation opinions, requiring that they be excluded.

III. PLAINTIFFS FAIL TO SHOW THAT DR. SMITH-BINDMAN'S META-ANALYSIS WAS BASED ON A VALID METHODOLOGY.

As explained in defendants' opening brief, Dr. Smith-Bindman concluded that "regular" talc use is associated with a 50% increased risk of HGSOC via a

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182 (*Id.*)

conclusion-driven meta-analysis that was riddled with subjective determinations and mistakes.[183] Plaintiffs begin by effectively abandoning Dr. Smith-Bindman's meta-analysis, stating that she "would have reached the same conclusions even without the meta-analysis she performed."[184] Plaintiffs otherwise fail to show that Dr. Smith-Bindman's meta-analysis was reliably conducted.

First, plaintiffs attempt to deny that Dr. Smith-Bindman conducted an unreliable post-hoc analysis by claiming that she was either too unfamiliar with the literature to cherry-pick studies, did not inspect the data before selecting which studies to focus on, or had "sound" reasons for excluding certain studies.[185] None of this is correct.

Dr. Smith-Bindman conducted an unreliable post-hoc analysis because she reviewed the literature and developed her conclusion before selecting which data to focus on.[186] Plaintiffs do not actually contest this. Plaintiffs contend that Dr. Smith-Bindman's "decision to focus on 'regular use and HGSOC' . . . occurred no

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183 (Defs.' Br. at 95-108.)

184 (Pls.' Opp'n at 192.)

185 (*Id.* at 193-96.)

186 (Defs.' Br. at 96-101.) The testimony plaintiffs cite only confirms this. (*See, e.g.*, Pls.' Opp'n at 191 ("As clarified in her deposition, 'the direction that my review took was partly informed by having read through a number of articles on the topic.'") (quoting Dep. of Rebecca Smith-Bindman, M.D. Vol. I ("Smith-Bindman 2/7/19 Dep.") 146:13-19, Feb. 7, 2019 (attached as Ex. B40 to Tersigni Cert.)).)

later than the second step of her methodological process," i.e., after she had performed a "literature search" and "review of the literature abstracts."[187] But by then it was too late. Courts reject post-hoc analyses like Dr. Smith-Bindman's because they enable an expert to "identify[] [a] conclusion" before deciding which studies to include, *Bextra*, 524 F. Supp. 2d at 1176, and such an approach does not constitute "performing scientific analysis in a prospective, unbiased manner," *Bracco*, 627 F. Supp. 2d at 452; *see also, e.g.*, *Snodgrass v. Ford Motor Co*., No. 96-1814(JBS), 2002 WL 485688, at *12 (D.N.J. Mar. 28, 2002) (excluding expert who "determined the conclusion before the hypothesis was put forth"). In short, the fact that Smith-Bindman's decision to focus on HGSOC occurred "before data was abstracted" is irrelevant because plaintiffs concede that she had read the "abstracts" at the front of each study, which provide the bottom-line results of each relevant study.[188] Moreover, the abstracts of most of the studies Dr. Smith-Bindman chose previewed the theory that there may be a higher association for HGSOC.[189]

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187 (Pls.' Opp'n at 190-91 (quoting Defs.' Br. at 98).)

188 (*Id.* at 191.)

189 *See, e.g.*, Gertig 2000 at 249 (background) (reporting odds ratios in abstract and noting that "[t]here was a modest elevation in risk for . . . invasive serous ovarian cancer").

Plaintiffs also deny that Drs. Smith-Bindman unreliably omitted studies that met her inclusion criteria, but fail to provide an explanation for her exclusion of Rosenblatt 2011 and ignore that including this study would have prevented her from claiming that there is a 50% risk increase for HGSOC. This sort of omission is a serious red flag because it suggests manipulation of the relevant data.[190] For this reason, too, plaintiffs fail to show that Dr. Smith-Bindman's work was reliable.

Second, plaintiffs utterly fail to refute that Drs. Smith-Bindman's definition of "regular use" was subjective and unreproducible. *See, e.g., In re TMI Litig.*, 193 F.3d 613, 703 n.144 (3d Cir. 1999) (expert opinions based on "subjective methodology" are inadmissible because "the only person capable of testing or falsifying the hypothesis is the creator of the methodology"), *amended in nonmaterial part*, 199 F.3d 158 (3d Cir. 2000). This challenge is the antithesis of a "challenge . . . to [Dr. Smith-Bindman's] conclusions," which plaintiffs accuse defendants of engaging in.[191] Defendants explained in detail that Dr. Smith-

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[190] (*See* Defs.' Br. at 95, 99; Pls.' Opp'n at 191-92.) Plaintiffs fail to distinguish defendants' cases (*see* Pls.' Opp'n at 190 n.512), which show that arbitrarily excluding relevant data is a hallmark of unreliability, *see, e.g., Zoloft I*, 26 F. Supp. 3d at 462 (excluding an expert for basing his opinion on a "self-selected subset of supportive studies, not the totality of the epidemiological evidence"); *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 268 (2d Cir. 2002) (excluding expert who "did not find it necessary" to include additional data although it was available) (citation omitted).

[191] (Pls.' Opp'n at 193-94.)

Bindman's ***methodology*** entailed defining "regular use" in an ad hoc manner requiring numerous judgment calls according to vague criteria she never defined – despite "several paragraphs within her report" purporting to do so.[192] For example, it is impossible to replicate Dr. Smith-Bindman's decisions regarding, *inter alia*, whether a study's "description made it clear" that it reported on "regular use"; when data on ever/never use "may have reflected daily use"; or how large a subgroup had to be to be "meaningful" – all of which are steps in the methodology Dr. Smith-Bindman outlines in her report.[193] Plaintiffs do not address these issues or the fact that this approach enabled Dr. Smith-Bindman to omit the Gates 2010 cohort study, which would have undermined her thesis.[194]

Third, plaintiffs do not refute that Dr. Smith-Bindman's results have a high error rate due to numerous data inaccuracies.[195] *See, e.g.*, *In re TMI Litig. Cases Consol. II*, 911 F. Supp. 775, 795-96 (M.D. Pa. 1996) (excluding expert who used subjective techniques that "expose[d] [his] methodology to a potentially high rate of error"). The explanations plaintiffs provide for the inaccuracies do not refute

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192 (*See id.* at 193.)

193 (Defs.' Br. at 101-02 (quoting Smith-Bindman Rep. at 32).)

194 (*Id.* at 103.) Plaintiffs instead incorrectly claim that defendants only criticized Dr. Smith-Bindman's "decision to define and apply 'regular use'" and that Dr. Smith-Bindman and her assistant were able "to reproduce the results." (Pls.' Opp'n at 193.) Neither is true, as set forth herein.

195 (*See* Defs.' Br. at 103-06.)

that Dr. Smith-Bindman's analysis contained them or contest that many were the result of subjective "estimation[]."[196] Finally, plaintiffs' claim that Dr. Smith-Bindman applied "the same rigor as if she were preparing a published report,"[197] ignores that Dr. Smith-Bindman wrote that she was conducting "a review for a legal case and d[id]n't need quite the detail I would usually need for a paper."[198]

For all of these reasons, Dr. Smith-Bindman's meta-analysis should be excluded.

IV. PLAINTIFFS FAIL TO REFUTE THAT THEIR EXPERTS' CAUSATION OPINIONS CONTROVERT THE SCIENTIFIC CONSENSUS AND THEIR NON-LITIGATION VIEWS.

Defendants also explained in their opening brief that plaintiffs' experts' opinions are unreliable because they contradict the scientific consensus and the views the same experts have published outside of litigation.[199] This argument has

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196 (*See* Pls.' Opp'n at 194-95.) Although Dr. Smith-Bindman attempted to explain the fact that none of the confidence intervals she used matched those in the underlying studies, this should be ignored because she improperly contacted her assistant during an overnight deposition break that defendants accommodated due to her claimed concussion. (Defs.' Br. at 105 n.250.) Plaintiffs do not attempt to defend this. And plaintiffs' argument that the "estimations did not relate to the abstraction of data" (Pls.' Opp'n at 195), even if it were true, would not refute that Dr. Smith-Bindman instructed her assistant to conduct subjective "estimation[]" as part of the methodology.

197 (*Id.* at 196.)

198 (Smith-Bindman 2/7/19 Dep. 77:14-18.)

199 (Defs.' Br. at 108-19.)

only grown stronger since defendants filed their opening brief. After all, just last month Dr. Siemiatycki co-authored a paper that listed ***suspected*** ovarian cancer risk factors and did ***not*** include talc.[200] This speaks volumes about the litigation-focused nature of plaintiffs' experts' opinions.

Plaintiffs' arguments in response lack merit.

First, plaintiffs incorrectly portray defendants as arguing that "the scientific community has reached consensus that talcum powder does not cause ovarian cancer."[201] But that is not what defendants said; rather defendants argued that the scientific community has stated that there is "inadequate," "limited" or inconclusive evidence of causation – a prevailing view that ***is*** at odds with plaintiffs' experts' opinions that external talc usage is a ***likely*** cause of ovarian cancer.[202]

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200 Leung et al., *Shift Work Patterns, Chronotype, and Epithelial Ovarian Cancer Risk*, Cancer Epidemiol Biomarkers Prev. 987, 987 (2019) (attached as Ex. A189 to 2d Suppl. Tersigni Cert.). The article did list "older age, never use/short duration of oral contraceptives, low parity, personal history of breast cancer, family history of breast or ovarian cancer, use of hormone replacement therapy, increased height, and a high body mass index." *Id.* Notably, Dr. Siemiatycki is one of the authors of the study who specifically contributed to the "[w]riting, review, and/or revision of the manuscript." *Id.* at 994 (emphasis omitted).

201 (Pls.' Opp'n at 197.)

202 2019 NCI PDQ ("weight of the evidence does not support an association" between external talc use and increased risk of ovarian cancer); FDA Denial Letter at 1 (FDA "did not find that the data submitted presented conclusive evidence of a causal association between talc use in the perineal area and ovarian cancer.");

(cont'd)

Plaintiffs nevertheless argue that IARC's classification of talc as "possibly carcinogenic" and the FDA's finding that the data are "not conclusive" "hardly 'contradict'" their experts' opinions.[203] Not so. IARC's classification of talc as a "*Group 2B*" agent that is "*possibly carcinogenic*" – the same classification it gives, *inter alia*, to pickled vegetables, ginkgo biloba and aloe vera whole leaf extract – means that it found only "***limited***" evidence of carcinogenicity.[204] That is in direct contrast to plaintiffs' experts' view that talc is a ***likely*** cause of ovarian cancer.[205] If IARC agreed with the bottom-line conclusions being offered by plaintiffs' experts in this litigation, it would have presumably designated talc as a "probable"

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IARC 2010 Monograph at 413 ("the epidemiological studies taken together provide *limited evidence* of an association between perineal use of talc-based body powder and an increased risk for ovarian cancer"); Draft Screening Assessment at 28 (classifying talc use as only a "potential concern for human health"); *see also* Langseth 2008 at 359 (noting that the "current body of experimental and epidemiological evidence is insufficient to establish a causal association").

203 (Pls.' Opp'n at 197.)

204 *See* IARC 2010 Monograph at 412-413 (bold emphasis added).

205 Plaintiffs ignore that IARC found the evidence of dose response "inconsistent"; noted that "chance, bias or confounding could not be ruled out with reasonable confidence"; and recognized that "[t]he limited number of studies available on the genetic toxicity of talc in vitro gave negative results." IARC 2010 Monograph at 31, 411-12.

carcinogen – not just a "possible" one.[206] Similarly, plaintiffs' reliance on the FDA letter only underscores the outlier approach taken by their experts in this litigation given the FDA's determination that the scientific evidence is insufficient to support the conclusion that talc causes ovarian cancer (or, for that matter, to support the conclusion that the Products contain asbestos or that talc is carcinogenic).[207]

While plaintiffs also repeatedly argue that their experts' causation opinions "closely align" with Health Canada's Draft Screening Assessment,[208] their reliance on that document continues to be fundamentally misplaced.[209] After all, far from reaching a definitive conclusion on causation, Health Canada merely states that the body of talc literature supports classifying talc use as a "***potential concern*** for human health."[210] Moreover, plaintiffs once again ignore that Health Canada

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206 This further illustrates how Dr. Siemiatycki's litigation opinions contradict his professional work, since he was chair of the IARC working group. (*See* Siemiatycki Rep. at 3.) While Dr. Siemiatycki attempts to reconcile his causation opinion with his IARC work by referring to intervening developments in the science (*id.* at 67-68), the reality is that post-2008 developments – including results of three cohort studies showing no association between external talc use and ovarian cancer – further weigh ***against*** a causal conclusion.

207 *See generally* FDA Denial Letter.

208 (Pls.' Opp'n at 197; *see also id.* at 84-91.)

209 Plaintiffs accuse defendants of ignoring the Draft Screening Assessment, but defendants addressed it at length. (*See* Defs.' Br. at 111-13.)

210 Draft Screening Assessment at iii, 28 (emphasis added).

expressly applies "[p]recaution . . . to avoid the potential underestimation of risk due to a lack of information, thus ***erring on the side of being protective of human health*** and the environment."[211] The limited analysis of the Bradford Hill factors in the Draft Assessment that plaintiffs highlight[212] was expressly conducted in light of this purpose.[213] It is thus inapposite for establishing causation in litigation (or science), as even plaintiffs' own authority shows. *See Roundup*, 2018 WL 3368534, at *1-2 (IARC's conclusion that chemical is "probably carcinogenic" was "insufficient to get the plaintiffs over the general causation hurdle" in part because "the public health inquiry does not map nicely onto the inquiry required by civil litigation").[214]

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211 Health Canada, *Application of Weight of Evidence and Precaution in Risk Assessment* (last updated June 15, 2017) (emphasis added), https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/application-weight-of-evidence-precaution-risk-assessments.html (attached as Ex. A57 to Tersigni Cert.).

212 (Pls.' Opp'n at 87-90.)

213 Draft Screening Assessment at 2 ("This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and ***incorporating a weight of evidence approach and precaution***.") (emphasis added).

214 (*See also* Defs.' Br. at 112-13 (collecting cases holding similarly).) While plaintiffs insinuate in a footnote that defendants are improperly trying to influence Health Canada (*see* Pls.' Opp'n at 87 n.267), plaintiffs ignore that their own experts have written to Health Canada seeking to advance their litigation views. *See* Email Submission of Anne McTiernan, M.D., Ph.D. to Health Canada, Feb. 5, 2019 (attached as Ex. F1 to Tersigni Cert.); Email Exchange between Anne

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Finally, in an attempt to fabricate agreement between outside researchers and plaintiffs' experts, plaintiffs argue that various entities have recognized talc as a "risk factor" for ovarian cancer and that such recognition is tantamount to a finding of causation because "[c]ause and risk factor are often used interchangeably."[215] Not so. Courts recognize that "risk factor" and "cause" are not one and the same. *See Wannall v. Honeywell Int'l, Inc.*, 292 F.R.D. 26, 41-42 (D.D.C. 2013) (explaining that studies stating "that consuming alcohol raises one's risk of developing various cancers . . . is not the same thing as saying that alcohol causes cancer"; "If exposure to a substance is a risk factor for a health outcome, that typically means that exposure to the substance has been associated with that health outcome at a particular level of statistical significance, but correlation does not imply causation.") (citations omitted), *aff'd sub nom. Wannall v. Honeywell, Inc.*, 775 F.3d 425 (D.C. Cir. 2014); *Braglin v. Lempco Indus., Inc.*, No. 06-CA-1, 2007 WL 1203853, at *4 (Ohio Ct. App. Apr. 24, 2007) ("Risk factor is an assessment of statistical association" that "does not necessarily indicate direct

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McTiernan, M.D., Ph.D. and Scott Hancock, Health Canada, Feb. 21, 2019 (attached as Ex. F3 to Tersigni Cert.); Letter from Jack Siemiatycki, M.Sc., Ph.D. to Health Canada, Feb. 6, 2019 (attached as Ex. F2 to Tersigni Cert.); Email Exchange between Jack Siemiatycki, M.Sc., Ph.D. and Scott Hancock, Health Canada, Mar. 2019 (attached as Ex. F5 to Tersigni Cert.).

[215] (Pls.' Opp'n at 60-65.)

cause . . . ."). The fact that plaintiffs stretch to equate these distinct concepts only further underscores their inability to defend their experts' causation opinions.

Second, plaintiffs also attempt to recast Drs. Siemiatycki and Moorman's contradictory pre-litigation published opinions by cherry-picking certain observations in those prior materials that supposedly are consistent with their opinions in this litigation.[216] This effort fails too.

Plaintiffs highlight a couple of snippets of qualified observations in the Langseth 2008 paper (co-authored by Dr. Siemiatycki), but omit the study's fundamental conclusion that the "current body of experimental and epidemiological evidence is ***insufficient to establish a causal association*** between perineal use of talc and ovarian cancer risk."[217] With respect to Dr. Moorman, plaintiffs similarly ignore her publications to the effect that neither ovarian cancer nor peritoneal cancer "was found to be associated with talc use."[218] Instead,

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216 (Pls.' Opp'n at 198-200.)

217 Langseth 2008 at 359 (emphasis added). The cherry-picked observations plaintiffs mention – that IARC classified talc as "possibly carcinogenic" and that the Langseth study stated that the "mechanism of carcinogenicity ***may*** be related to inflammation" (Pls.' Opp'n at 199 (emphasis added) (quoting Langseth 2008 at 360)) – do not support their experts' opinions, as defendants have explained.

218 Grant et al., *Primary Peritoneal and Ovarian Cancers: An Epidemiological Comparative Analysis*, 21 Cancer Causes Control 991, 996 (2010) (attached as Ex. A50 to Tersigni Cert.). (*See also* Dep. of Patricia G. Moorman, M.S.P.H., Ph.D. ("Moorman Dep.") 138:13-15, Jan. 25, 2019 (attached as Ex. B39 to Tersigni Cert.)
(cont'd)

plaintiffs focus on isolated statements in the subsequent Schildkraut 2016 study, published after Dr. Moorman became involved in litigation,[219] that "indicated that talc was a 'modifiable risk factor' for ovarian cancer and that the association seen in the case control studies (including hers) [was] not likely to be the result of recall bias."[220] Of course, the more recent 2016 study says nothing about Dr. Moorman's earlier published views on the causation question. In any event, plaintiffs' characterization of the 2016 study is erroneous in light of the actual data underlying it, which do in fact demonstrate recall bias (essentially, the propensity for study participants to over-report past talc use).[221] And although plaintiffs claim that Dr. Siemiatycki and another expert (Dr. McTiernan) have "expressed their views outside litigation,"[222] they omit that this occurred very recently, presumably

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(admitting that in her 2009 study, she found "little evidence of an association [between talc and ovarian cancer]").)

219 Dr. Moorman had already been solicited by lawyers for talc plaintiffs to become a litigation expert by the summer of 2016, before the Schildkraut paper was published (in October of that year). (*See* Moorman Dep. 11:5-19.) The Schildkraut paper does not disclose this fact. *See* Schildkraut 2016 at 1416 (disclosing no conflicts of interest).

220 (Pls.' Opp'n at 199.)

221 (*See id.*) *See also* Schildkraut 2016 at 1414 tbl. 2 (reporting, for post-2014 and pre-2014 interviewees, respectively, 51.5% versus 36.5% talc use and relative risks of 2.91 (95% CI 1.70-4.97) versus 1.19 (95% CI 0.87-1.63)).

222 (Pls.' Opp'n at 198.)

in coordination with plaintiffs' counsel, to support plaintiffs' litigation position. *See Lust ex rel. Lust v. Merrell Dow Pharm., Inc.*, 89 F.3d 594, 597 (9th Cir. 1996) (rejecting expert testimony as unreliable where expert "published the 1984 article . . . [when] he was at that time already a professional plaintiff's witness").[223]

Plaintiffs alternatively argue that "enough evidence has accumulated through 2019" such that Drs. Moorman and Siemiatycki's shift in opinion is justified.[224] But this last-ditch argument fares no better. The evidence that has "accumulated" since Dr. Siemiatycki published that there was "insufficient" evidence of causation in 2008 includes: (1) three reports on large cohort studies showing null results, with one identifying douching as a previously unstudied confounder and another erasing a previously reported increased risk of HGSOC;[225] (2) additional case-control studies that have continued to report weak associations, including one that

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[223] In fact, as explained in the General Causation Brief, Dr. McTiernan's Congressional testimony merely parroted her expert report in this matter.

[224] (*See, e.g.*, Pls.' Opp'n at 197-98.) Dr. Siemiatycki has conceded that the overall magnitude of the association has ***decreased*** as more evidence has accumulated. (*E.g.*, Siemiatycki Dep. 149:14-150:3.)

[225] Gates 2010; Houghton 2014; Gonzalez 2016. A non-litigation analysis presumably would have found these additional studies particularly important given that Dr. Siemiatycki and his co-authors wrote in 2008 that the single existing cohort study (Gertig 2000) was "arguably the strongest study because of its partly prospective ascertainment of exposure." Langseth 2008 at 358.

demonstrated recall bias;[226] (3) meta-analyses that have reflected the same weak aggregate association;[227] and (4) conclusions by public health authorities that there is ***insufficient*** evidence of causation.[228] Presumably, this is why Dr. Siemiatycki's most recent co-authored publication does ***not*** mention talc as a potential ovarian cancer risk factor, as discussed *supra*. In short, plaintiffs' attempt to justify Drs. Siemiatycki and Moorman's newfound support for plaintiffs' litigation position based on recent evidence should be rejected.

CONCLUSION

For the foregoing reasons and those set forth in defendants' opening brief, the Court should exclude plaintiffs' experts' general causation opinions.

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226 *See, e.g.*, Schildkraut 2016 at 1416. Notably, one post-2008 case-control study (Rosenblatt 2011) contradicts the notion of a dose response, as it reported ***negative*** associations between talc use and ovarian cancer for women who used talcum powder between 4,800 and 9,999 lifetime applications and for women with more than 10,000 lifetime applications. Rosenblatt et al., *Genital Powder Exposure and the Risk of Epithelial Ovarian Cancer*, 25(2) Cancer Causes Control 737, 740 tbl. 2 (attached as Ex. A125 to Tersigni Cert.).

227 Berge 2018; Penninkilampi 2018. One of these meta-analyses even "confirmed the trend toward lower overall risk estimates as more evidence accumulated" and stated that the data do "not support a causal interpretation of the association." Berge 2018 at 253, 256.

228 *E.g.*, FDA Denial Letter at 1; 2019 NCI PDQ.

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Respectfully submitted,

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